STEREOCHEMISTRY OF THE CYCLOPROPYL-ALLENE CONVERSION AND CONFIGURATIONAL STABILITY OF 2,2-DIPHENYLDIAZOCYCLOPROPANE

By

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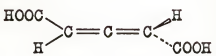
CHAPTER I

THE STEREOCHEMISTRY OF THE CYCLOPROPYL-ALLENE TRANSFORMATION

Introduction

The X-ray determination of the absolute configuration of (+)-tartaric acid by Bijvoet *et al.*[1] constitutes the first determination of the absolute configuration of an organic molecule and provides a point of reference for the determination of absolute configuration of any organic compound containing one or more asymmetric carbon atoms. Another important stereochemical problem is the assignment of absolute configuration to optically active compounds which do not possess asymmetric carbon atoms (axially dissymmetric compounds[2]) by configurational correlation with tartaric acid. The most common organic compounds which fall into this category are the biphenyls, allenes, alkylidenecycloalkanes and spiranes. Methods have been recently developed for obtaining the absolute configuration of biphenyl derivatives[3] and some progress has been made on the allene problem although two of the three published[4,5] absolute configuration assignments must be regarded as tentative since they require not only mechanistic assumptions but partially rely on physical methods which have been shown to

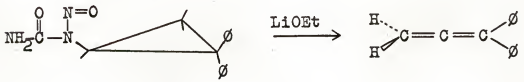
be unreliable.[6] The only unequivocal chemical correlation is the assignment of absolute configuration to (−)-glutinic acid (I).[7]



(−)-I

The method employed in this correlation, while ingenious, is severely limited not only by the fact that the allene under study must be resolvable, but more importantly, that the method is essentially specific for compound I. It would be desirable to find a correlation sequence leading to optically active allenes which is general and which does not require the optical fractionation of the allene.

A series of papers from these laboratories[8] describe the preparation of 1,1-diphenylallene (III) from the reaction of 2,2-diphenylcyclopropylnitrosourea (II) with lithium ethoxide.



II III

This transformation of a cyclopropyl compound to an allenic product would serve as a general method for the determination

of the absolute configuration of allenes provided that the following criteria are met: 1) the cyclopropyl precursor is obtainable in an optically active form; 2) the cyclopropyl compound is suitably substituted so as to give an allenic product devoid of any symmetry elements; 3) the absolute configuration of the cyclopropyl precursor is known or can be unequivocally determined; 4) there is a significant degree of asymmetric induction in the transformation which results in the production of an allene of measurable optical activity; and, 5) the absolute stereochemistry of the cyclopropyl-allene transformation is known.

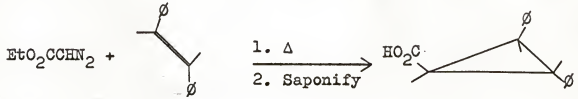
In the early stages of this work a system was developed which demonstrates that criteria 1, 2, and 4 can be met in the laboratory. Experiments were then devised to show that criteria 3 and 5 were experimentally feasible.

Results and Discussion

The trans-2,3-diphenylcyclopropyl system was chosen to demonstrate the feasibility of the conversion of a cyclopropyl precursor to an optically active allene. This system was chosen because the preparation and resolution of the starting material, trans-2,3-diphenylcyclopropanecarboxylic acid (IV), has been published[9] and it was felt that this material could be converted, using the reported experimental conditions[8] for the closely analogous

2,2-diphenylcyclopropyl system, to an allene precursor and ultimately to an optically active allene.

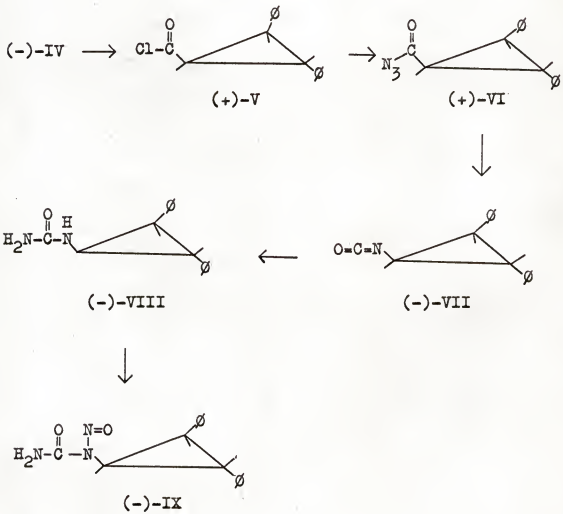
The starting material (IV) was obtained by a modification of the literature procedure[9] from the thermal decomposition of ethyl diazoacetate in the presence of trans-



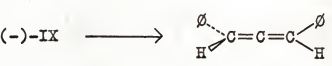
IV

stilbene. It was converted to the corresponding acid chloride (V) by treatment with thionyl chloride and the acid chloride was converted to the corresponding acid azide (VI) by treatment with saturated aqueous sodium azide at 0°. Heating the acid azide (VI) in refluxing benzene effected a Curtius rearrangement yielding the expected isocyanate (VII) which was aminated at 0° to give trans-2,3-diphenylcyclopropylurea (VIII) in approximately 60 per cent yield from the starting acid. The urea (VIII) was converted to the corresponding nitrosourea (IX) in 40 per cent yield by treatment with nitrous acid at 0°. Decomposition of the purified nitrosourea (IX) by lithium ethoxide in n-heptane at 0° yielded 1,3-diphenylallene (X) in approximately 80 per cent yield. The physical constants of this material agreed with those published for 1,3-diphenylallene.[10]

Optically active trans-2,3-diphenylcyclopropylcarboxylic acid (IV) was then obtained by resolution via the quinine salts. The optically active acid was then converted to optically active N-nitroso-N(trans-2,3-diphenylcyclopropyl)urea (IX) employing the same sequence used to obtain the racemic nitrosourea (IX) from the racemic acid (IV).



The optically active nitrosourea (-)-IX, was then converted to 1,3-diphenylallene employing the same conditions used to effect the same transformation in the racemic series. Isolation and rotation analysis of the crude allene showed the material to have a specific rotation of +419°. One recrystallization from pentane gave (+)-1,3-diphenylallene with the surprisingly high specific rotation of +797°. These findings have been recently reported



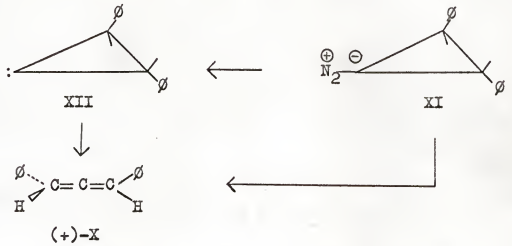
X

$[a]_D^{24}$ +797°

in the literature in the form of a preliminary communication.[11] This compound has been previously prepared[10] by the asymmetric rearrangement of 1,3-diphenyl-1-propyne on an alkaloid-impregnated alumina column; the 1,3-diphenylallene obtained had a specific rotation of + 2.48°.

Having demonstrated that criteria 1,2 and 4 are experimentally feasible, it is of interest to explore criteria 3 and 5. First of all, the precursor or precursors to the allene (X) have not been conclusively determined. However, by analogy to the base-induced decomposition of N-nitroso-N-(2,2-diphenylcyclopropyl)urea (II),[8] the reaction scheme most likely involves initial formation of the

diazocyclopropane (XI) which can either decompose in a concerted fashion to the allene or proceed first to the



cyclopropylidene (XII) that can then collapse to give the allene.

Secondly, it is of interest to examine what the retention of asymmetry in the allene (X) means with regard to the more intricate details of the formation of the compound from its precursors. Some insight can be gained by considering individually the various structural and geometrical changes which must occur as demanded by the geometry of the product during the conversion of either the diazocyclopropane (XI) or the cyclopropylidene (XII) to (+)-1,3-diphenylallene (X). Four changes of real significance must take place. The bond between C_2 and C_3 (Figure 1) must break, the angles β must increase from about 150° to 180°, the angle α must increase from 60° to 180°, and,

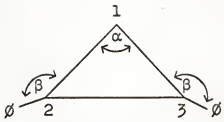


Figure 1

finally planes A and B (Figure 2) must rotate 90° with respect to each other.

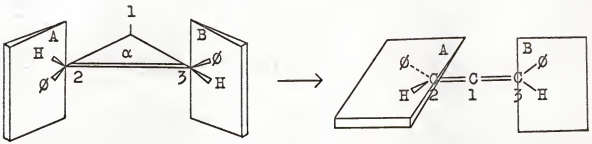


Figure 2

If the angles α and β increase to 180°, thus making carbons 1,2 and 3 collinear, before any rotation of planes A and B occurs, the allene must be optically inactive since this sequence entails an intermediate which possesses a plane of symmetry. Thus, the mere fact that the allene obtained is optically active demonstrates unequivocally that some rotation of planes A and B must occur before α and β increase to 180°.

The fact that rotation of the two planes precedes collinearity of carbons 1, 2 and 3 suggests that the source

of the asymmetric induction leading to an optically active product resides in steric effects that affect the direction of rotation of the planes A and B.

To illustrate the important steric effects, the concerted decomposition of only the diazocyclopropane (XI) will be discussed. However, it should be kept in mind that the same arguments also hold for opening the cyclopropylidene ring (XII) except that the leaving nitrogen would be replaced by a pair of electrons. For the sake of simplicity, assume that the groups on carbon 3 are held in place (Figure 3) and let the entire rotation of the planes take place

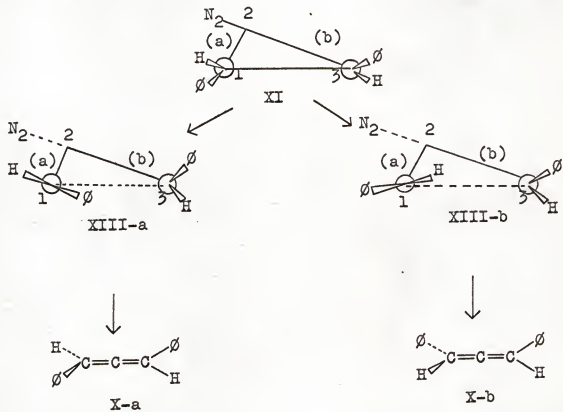
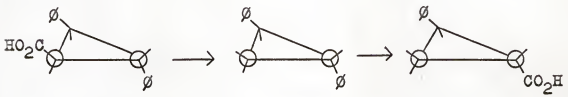


Figure 3

around bond (a). It can be seen that counterclockwise rotation of the substituents on carbon 1 leads to the intermediate XIII-a in which the phenyl on carbon 1 experiences interactions with the phenyl and hydrogen on carbon 3 while the hydrogen on carbon 1 is opposed to the leaving nitrogen on carbon 2. The net result is the formation of enantiomer X-a. Alternatively, if the substituents on carbon 1 are rotated in a clockwise manner around bond (a) to give intermediate XIII-b, the hydrogen on carbon 1 experiences interactions with the phenyl and hydrogen on carbon 3 and the phenyl is opposed to the leaving nitrogen and the net result is the formation of the other enantiomer, X-b. Clearly, then, if steric interactions with the leaving nitrogen are less important than with the phenyl and hydrogen on carbon 3, the clockwise rotation will be preferred and enantiomeric allene X-b will be the predominant product. And, of course, if the converse were true the other enantiomer (X-a) would be the predominant product.

We have found, and recently reported,[12] that the former of these two possibilities actually occurs. This conclusion is based on the assignments of absolute configuration to (-)-trans-2,3-diphenylcyclopropanecarboxylic acid (IV) and (+)-1,3-diphenylallene (X). Professor S. F. Mason has assigned structure X-b as the absolute configuration of (+)-1,3-diphenylallene using circular dichroism

measurements.[13] The correlation scheme used for assigning the absolute configuration to the cyclopropane acid (IV) is depicted in Figure 4.



(-)-IV (-)-XIV (-)-XV

Figure 4

The (-) acid (IV) was refluxed with quinoline and copper chromite catalyst for six hours. Removal of unreacted starting material afforded (-)-trans-1,2-diphenylcyclopropane (XIV) in 43 per cent yield, $[a]_D^{20}$ -30.9°. The physical constants of this material were in agreement with those published[14] for the authentic racemic hydrocarbon. After the results of this correlation scheme were in press,[12] a communication appeared assigning the absolute configuration of (+)-XIV as (+)-S[15] which is in agreement with the above findings. (-)-XIV was degraded by ozonolysis in glacial acetic acid. Oxidative workup of the reaction mixture with hydrogen peroxide gave an oil which was crystallized from water. The resulting crystalline solid

obtained proved to be (-)-XV as shown by comparison of physical properties with authentic racemic XV. The absolute configuration of (-)-XV has been recently shown to be 1R:2R.[16]

These results, then, establish the absolute stereochemistry of the cyclopropyl-allene transformation -- a transformation whose stereochemistry can be rationalized on simple steric grounds.

It was suggested[17] that the direction of ring opening of a cyclopropylidene or diazocyclopropane could be controlled by electronic effects rather than steric effects. Woodward and Hoffman in a recent publication[18] point out that substituents in ring opening reactions can undergo either conrotatory or disrotatory modes of rotation depending upon orbital symmetries. This correlation does not apply to systems with an even number of cumulated double bonds since rotation in the disrotatory sense would not give a system in which the terminal groups are orthogonal to each other, a factor which is demanded by the geometry of the allene. Furthermore, it is not possible to predict by the Woodward and Hoffman method which direction of conrotatory ring opening would be preferred. Private communication with one of the authors[19] of the publication on the electronic basis of ring opening substantiates these views.

An attempt was made, but not completed due to experimental difficulties, to obtain a configurational correlation based entirely upon chemical methods to determine the absolute stereochemistry of the cyclopropyl-allene transformation. The correlation scheme developed to determine the absolute stereochemistry of the cyclopropyl-allene transformation is depicted in Figure 5.

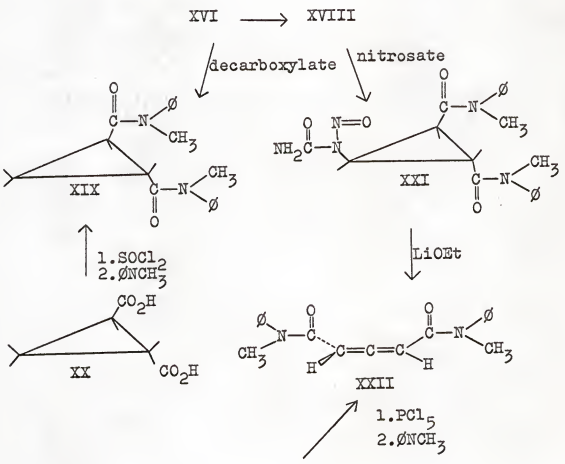
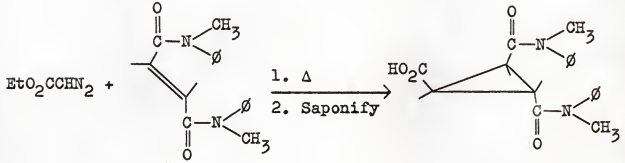


Figure 5

This scheme is based upon the known absolute configurations of (+)-trans-1,2-cyclopropanedicarboxylic acid (XX)[16] and (-)-1,3-pentadienedioic acid (I).[7] The following steps were successfully completed in the correlation scheme: 1) synthesis of XVI; 2) resolution of XVI; 3) XVI → XVIII; 4) XX → XIX; 5) I → acid chloride. The steps not completed due to experimental difficulties were: 1) XVIII → XXI, and 2) XXI → XXII. The conversion XVI → XIX was not attempted.

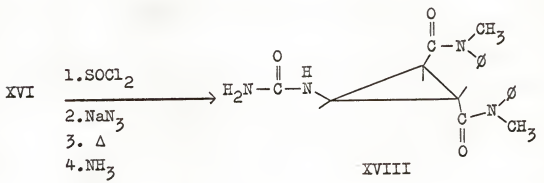
trans-2,3-Bis(N-methylcarboxanilido)cyclopropanecarboxylic acid (XVI) was obtained in approximately 25 per cent overall yield by thermally decomposing ethyl diazoacetate in the presence of bis-(N-methyl-N-phenyl)-fumaramide (XVII).



XVII XVI

The resolution of the starting acid (XVI) proved to be somewhat troublesome. Attempts to form crystalline salts with a series of optically active bases yielded uncrystallizable oils in all cases. The acid was finally resolved *via* a kinetic resolution using (-)-menthol.

The acid (XVI) was converted to the corresponding urea (XVIII) employing a sequence similar to that used in the analogous *trans*-2,3-diphenylcyclopropyl series.



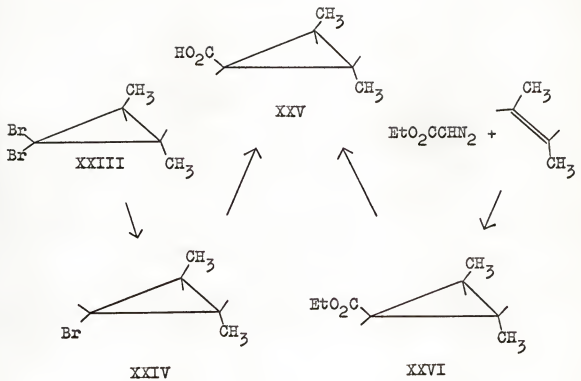
XVIII

Treatment of (+)-XX with thionyl chloride followed by N-methylaniline yielded (-)-XIX. It was found that when 1,3-pentadiendioic acid (I) was treated with thionyl chloride in an attempt to obtain the acid chloride that the product obtained did not show a 5.1 μ infrared absorption indicating that the allene linkage had been disrupted under the reaction conditions. It was subsequently found in a preliminary experiment that if I was treated with phosphorous pentachloride that a crude acid chloride was obtained which showed a 5.1 μ (allene) absorption and a

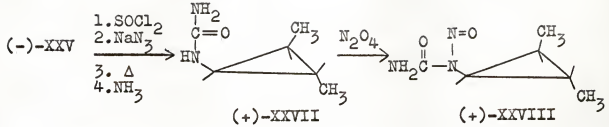
5.6 μ acid chloride carbonyl absorption and no absorptions due to carboxylic acid groups which is indicative of the formation of the diacid chloride of I.

However, attempts to nitrosate the urea XVIII with nitrous acid under various conditions yielded starting material in all cases. Numerous attempts at nitrosation of the urea using dinitrogen tetroxide gave gummy, dark brown solids with wide melting ranges. Repeated attempts to purify these materials yielded the starting crude nitrosoureas. The infrared spectra of these products showed a strong carbonyl absorption at 5.7 μ which is characteristic of a nitrosourea carbonyl group. Attempts at decomposing the crude nitrosation products with base yielded unidentified materials which did not show an infrared absorption at 5.1 μ, a peak which would be characteristic of the allene linkage in XXII.

The foregoing argument that the origin of the asymmetric induction resides in steric effects is supported in part by preliminary studies on the trans-2,3-dimethylcyclopropyl series. 1-Bromo-trans-2,3-dimethylcyclopropane (XXIV) was obtained from the known 1,1-dibromo-trans-2,3-dimethylcyclopropane (XXIII)[20] in 78 per cent yield via a selective reduction using tri-n-butyltin hydride. Carbonation of the Grignard reagent from the bromide (XXIV) yielded trans-2,3-dimethylcyclopropanecarboxylic acid (XXV) in 31 per cent yield.



Additional proof that XXV is the trans isomer is the fact that the acid was obtained from the ester (XXVI) resulting from the addition of ethyldiazoacetate to trans-2-butene, a carbene addition reaction which is known to be stereospecific. The carboxylic acid XXV was resolved via the quinine salts and the optically active acid (α_D^{17} -4.73°) was converted to the corresponding urea (XXVII (α_D^{20} +3.45). The urea was converted to the optically active nitrosourea (XXVIII) by treatment with dinitrogen tetroxide at -55°. The nitrosourea (XXVIII)



(α_D^{21} +2.69°) was dissolved in triethylene glycol and treated with lithium ethoxide at 0°. 1,3-Dimethylallene (XXIX) was isolated from the reaction mixture and was found

XXIX

to be optically inactive. This result supports the steric argument for asymmetric induction since it is well known that methyl groups have less steric bulk than phenyl groups and would be expected to exhibit less steric influence in structures such as XIII-a and XIII-b thus leading to an optically inactive product. This result must be regarded as tentative since the optical purity of the starting acid (XXV) is unknown. The quinine salt of the acid used in the transformation (-)-XXV → (+)-XXVII → (+)-XXVIII was crystallized once from acetone and a small portion was

recrystallized three times from acetone; essentially no change was noted in the rotation of the four crops of diastereomers and a sample of acid obtained from the final recrystallization of the quinine salt had essentially the same rotation as the starting acid (XXV) used to prepare the nitrosourea (XXVIII). Furthermore, the melting point of the diastereomer was not appreciably altered when the salt was recrystallized from other solvents. Although the foregoing tests meet the criteria of optical purity used by many workers, the method is by no means unequivocal.[21] Furthermore, the batch of optically active acid used to make the nitrosourea was 68 per cent of the starting amount of racemic acid used in the resolution, thus demonstrating that the acid (XXV) was at most 47 per cent optically pure. Further results must await an extensive investigation of the resolution of acid XXV in order to obtain the material in a higher degree of optical purity.

CHAPTER II

CONFIGURATIONAL STABILITY OF 2,2-DIPHENYLDIAZOCYCLOPROPANE

Introduction

The configurational stability of carbanions[24] has been a subject of recent study.[22] It has been shown that tetrahedral carbanions have very low configurational stability.[27] Reaction of optically active 2-octyl iodide (XXX) with butyl lithium followed by carbonation gave

$$CH_3\text{-}\underset{\underset{I}{|}}{C}\text{-}(CH_2)_6\text{-}CH_3 \xrightarrow[2.CO_2]{1.C_4H_9Li} CH_3\text{-}\underset{\underset{CO_2H}{|}}{C}\text{-}(CH_2)_6\text{-}CH_3$$

(-)-XXX (-)-XXXI

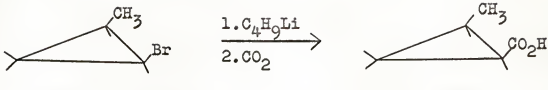
(-)-2-methyloctanoic acid (XXXI). Below -70° the reaction proceeded with approximately 20 per cent retention of configuration and above -70° the 2-octyl carbanion, when carbonated, yielded racemic acid (XXXI).[23]

In contrast to the configurationally unstable tetrahedral carbanions, it has been demonstrated that trigonal carbanions have considerable configurational stability.[25] One representative example of a configurationally stable trigonal carbanion is found in the work of Curtin and Crump.[25] These workers showed that when cis (or trans)-

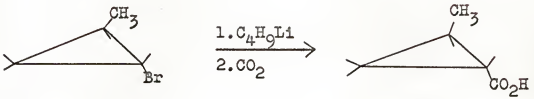
propenyl bromide is subjected to lithium-halogen interchange followed by treatment with benzaldehyde that complete overall retention of configuration is observed even at 35°. In fact, it has been estimated that the energy barrier for interconversion of some trigonal carbanions is as high as 25 to 35 kilocalories per mole.[26]

Since the cyclopropane ring is considered to have a great deal of double bond character, it has been of interest to examine the configurational stability of various cyclopropyl carbanions.[24] It has been postulated that the exo orbitals of cyclopropane are hybridized in a $sp^{2.28}$ manner. Since a pair of electrons in an sp^3 orbital (tetrahedral carbanion) has been shown to be of low configurational stability and a pair of electrons in a sp^2 orbital (trigonal carbanion) possesses high configurational stability, it would be predicted that a pair of electrons in an $sp^{2.28}$ orbital (cyclopropyl carbanion) might have an intermediate configurational stability.

Applequist and Peterson[28] demonstrated that treatment of cis (XXXII) or trans (XXXIII)-2-methylcyclopropyl bromide with butyl lithium at 0° followed by carbonation gave exclusively cis (XXXIV) and trans (XXXV)-2-methylcyclopropanecarboxylic acid respectively.

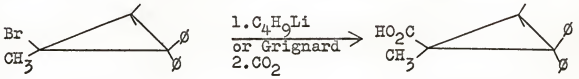


XXXII XXXIV



XXXIII XXXV

Walborsky and co-workers have shown that when 1-bromo-1-methyl-2,2-diphenylcyclopropane (XXXVI) was treated with butyl lithium[29] or converted to the corresponding Grignard reagent[29,30] and subsequently carbonated that

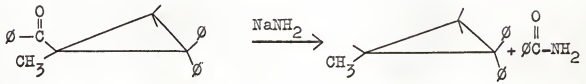


(-)-XXXVI (+)-XXXVII

1-methyl-2,2-diphenylcyclopropanecarboxylic acid (XXXVII) was obtained with 100 per cent retention of configuration.

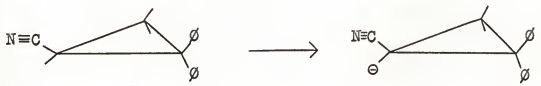
The Haller-Bauer cleavage[32] of optically active 1-methyl-1-benzoyl-2,2-diphenylcyclopropane (XXXVIII) was also studied. Treatment of the optically active ketone XXXVIII with sodium amide yielded 1-methyl-2,2-diphenylcyclopropane (XXXIX) with complete retention of configuration.[33] It has

been shown that the Haller-Bauer cleavage most likely involves a carbanionic intermediate.[34]



(-)-XXXVIII (+)-XXXIX

The 2,2-diphenylcyclopropyl cyanide (XL) system was also studied in an attempt to demonstrate the geometrical stability of the cyclopropyl carbanion. It was found that when the optically active nitrile (XL) was treated with lithium diisopropyl amide in ether for less than one minute at -76° and then hydrolyzed that the recovered nitrile (XL) was completely racemic.[35] However, further experiments with XL in hydroxylic solvents demonstrated that the half life for the rate of deuterium exchange at 75° in methanol-d is on the order of eight minutes[29] where-



(+)-XL XLI

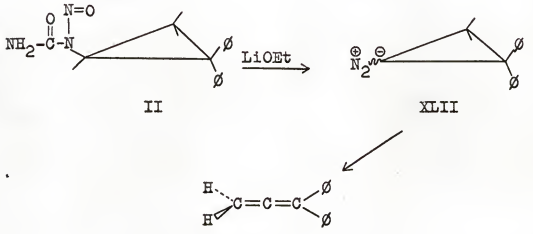
as the half life for racemization in methanol at 75° (0.992M sodium methoxide), is on the order of 540 hours.[35] The

authors propose[29] that these data indicate that there is an energy barrier to inversion and that the carbanion (XLI) has a finite lifetime.

In this work we have studied the configurational stability of a cyclopropyl intermediate with carbanionic character generated from the base-induced decomposition of N-nitroso-N-(2,2-diphenylcyclopropyl)urea (II).

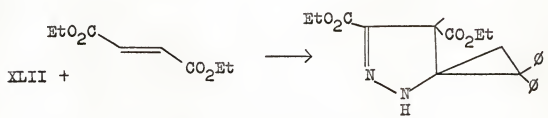
Results and Discussion

It has been shown that 2,2-diphenyldiazocyclopropane (XLII) is an intermediate in the base-induced decomposition in n-heptane at 0° of N-nitroso-N-(2,2-diphenylcyclopropyl)-urea (II) which leads to the production of 1,1-diphenyl-allene (III).[8]



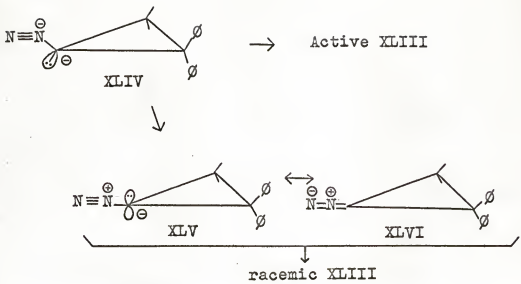
II XLII III

The existence of this intermediate was demonstrated by decomposing the nitroso compound (II) in the presence of diethyl fumarate and isolating the resulting pyrazoline (XLIII).[8]



XLIII

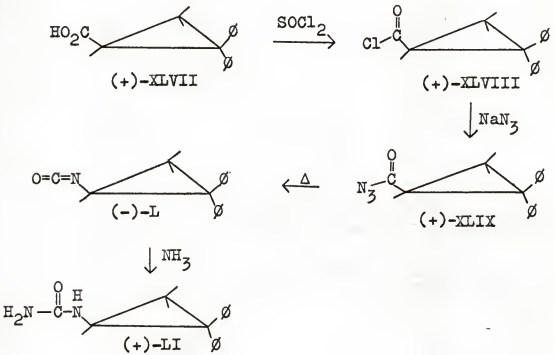
We felt it of interest to examine the configurational stability of the diazo compound (XLII). If the diazo maintains its configurational stability with <u>exo</u> $sp^{2.28}$ bonds (structure XLIV) then the subsequent reaction with diethyl fumarate should yield the pyrazoline (XLIII) in an optically active form. Alternatively, if the diazo compound initially formed (XLIV) rehybridizes to structure XLV (either as an energy minimum or the transition state in the rapid interconversion of XLIV to its enantiomeric form) in which the electron pair is in a p orbital before reaction with diethyl fumarate then the pyrazoline will be optically inactive since the trigonal diazo (XLV) possesses a plane of symmetry.[31]



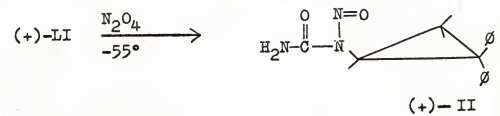
Since rehybridization of the orbital containing the electron pair from $sp^{2.28}$ (XLIV) to p (XLV) requires energy and also results in an increase of "I" strain, it might be predicted that the tetrahedral diazo (XLIV) would be the reactive species thus leading to an optically active product (XLIII). On the other hand, an increase in resonance stabilization of XLV by canonical form XLVI may tend to override the energy factors required for the rehybridization and increase in "I" strain in going from XLIV to XLV thus leading to an optically inactive product. This work shows that the latter of these two possibilities actually occurs.

2,2-Diphenylcyclopropanecarboxylic acid (XLVII) was prepared from diphenyldiazomethane and methyl acrylate using the published procedure.[27] The acid was resolved via the

quinine salts and converted via the acid chloride (XLVIII), acid azide (XLIX), and isocyanate (L) to the corresponding optically active urea (LI) using methods closely analogous to the published procedure[8] for obtaining the racemic urea (LI). The optically active urea (LI) was treated with



dinitrogen tetroxide at -55° and yielded optically active N-nitroso-N-(2,2-diphenylcyclopropyl)urea (II).



The optically active nitrosourea (II) was decomposed with lithium ethoxide in the presence of diethyl fumarate at 0° and the expected pyrazoline (XLIII) was isolated as in the literature procedure.[8] The physical constants of the pyrazoline (XLIII) obtained from the decomposition of optically active nitrosourea, (+)-II, were in agreement with those of the pyrazoline obtained from the decomposition of racemic nitrosourea, (+)-II.[8] Rotation analysis showed the pyrazoline obtained from (+)-II to be optically inactive thus demonstrating that the tetrahedral diazo (XLIV) is of low configurational stability and that the reactive species is most likely a resonance hybrid of XLV and XLVI.

CHAPTER III

EXPERIMENTAL

General.--Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Boiling points reported in this work are also uncorrected. The elemental analyses were performed by Dr. Harry W. Galbraith, Galbraith Laboratories, Incorporated, Knoxville, Tennessee. Infrared spectra were obtained by use of a Perkin-Elmer Model 137B Infracord spectrophotometer. Sampling modes are specified in the individual experiments. Ultraviolet determinations were run on a Cary Model 14 double beam recording spectrophotometer employing silica cells. Optical rotations were measured in one decimeter tubes with a Rudolph Model 80 high precision polarimeter. Gas-liquid chromatography was performed on two instruments manufactured by Wilkins Instrument and Research, Incorporated, Walnut Creek, California. The majority of the preparative work was accomplished on a Model A-350-B dual column, temperature programming gas chromatograph fitted with a thermistor detector and employing helium as the carrier gas. During the course of this work the instrument was fitted by the manufacturers with accessory

parts from a Model A-700 automatic preparative gas chromatograph which allowed automatic injection and collection of samples. The analytical gas-liquid chromatography was accomplished on a Model A-600-B "Hy-FI" gas chromatograph equipped with a hydrogen flame ionization detector and employing nitrogen as the carrier gas. Column specifications and operating conditions of these instruments are specified in the individual experiments. Analytical thin layer chromatography was accomplished on 2" x 8" plates coated in this laboratory with 0.25 mm. layers of Merck silica gel HF_{254} using ultraviolet detection unless otherwise specified. Nuclear magnetic resonance spectra were determined with a Varian 4300-2 high resolution spectrometer operating at 60 mc. Chemical shifts are reported in tau values from tetramethylsilane.

Ethyl diazoacetate.--One mole of the ester was prepared according to the procedure of Searle.[36] After drying the methylene chloride solution of the ester, the solvent was removed at room temperature using a stream of dry nitrogen. The resulting golden yellow oil was used directly in the preparation of 1-carboethoxy-2,3-diphenylcyclopropane.

1-Carboethoxy-trans-2,3-diphenylcyclopropane.--The procedure of D'yakonov[9] et al. was used with modifications. The reaction was run in a three-necked constant temperature

reaction apparatus. The n-butyl acetate-water azeotrope (72.8 parts ester:28.7 parts water) was used as the heat transfer medium (b.p. 90.2°). A solution of 100 g. (0.87 mole) of ethyl diazoacetate and 40 ml. of cyclohexane was added dropwise over a three hour period to a suspension of 144 g. (0.80 mole) of trans-stilbene and 3.2 g. of anhydrous copper sulfate in 120 ml. of cyclohexane. The reaction mixture was heated for an additional three hours after the addition period. The cyclohexane was then removed using a rotary evaporator. The reaction mixture was cooled to 0°, 300 ml. of ice-cold 95 per cent ethanol was added and the solid mass was stirred manually until the lumps were broken up. The unreacted stilbene was filtered off and triturated with 550 ml. of cold 95 per cent ethanol. After air drying the stilbene weighed 94.5 g. The ethanol was removed from the filtrate and the resulting dark oil was distilled using a 30 cm. Vigreaux column. The first fraction was diethyl fumarate, 23 g., b.p. 75-90° (2 mm.). A small amount of stilbene distilled in the range 145-160° (0.8 mm.) and 63 g. (86.5% based on reacted stilbene) of 1-carboethoxy-2,3-diphenylcyclopropane was collected in the range 161-175° (0.8 mm.); reported[9] b.p. 136-142° (0.2 mm.).

Trans-2,3-diphenylcyclopropanecarboxylic acid.--Saponification of 63 g. (0.237 mole) of the corresponding ethyl ester according to the literature procedure[9] yielded,

after recrystallization from 1:1 benzene petroleum ether, 39.1 g. (72.4%) of a crystalline white solid, m.p. 154-155°; reported[9] m.p. 153-154°.

Resolution of trans-2,3-diphenylcyclopropanecarboxylic acid.--Twenty-five grams of the acid was dissolved in 230 ml. of hot 95 per cent ethanol and quinine, 33.8 g., was dissolved in 230 ml. of hot 95 per cent ethanol. While hot, the acid solution was poured into the hot ethanolic quinine solution and the clear solution was heated on the steam bath for five minutes. The solution was cooled in ice and the resulting white precipitate was filtered and air dried. The diastereomeric mixture weighed 51.9 g., m.p. 208-228°. The solid was divided into two equal portions and each portion was extracted in a Soxhlet apparatus for 26.5 hours with 1400 ml. of 95 per cent ethanol. After standing at room temperature overnight, the resulting crystalline precipitates in the reaction flasks were filtered off, combined and air dried. After drying, 28.5 g. of a crystalline solid was obtained, m.p. 208-216°. The crystalline solid which remained in the thimbles was dried and combined; 8.1 g., m.p. 219-221.5°. Reported[9] m.p. 222-223°. The material from the reaction flasks was again extracted with 3000 ml. of 95 per cent ethanol for 23.5 hours, and after standing at room temperature overnight, 14.7 g. of white needles were obtained from the reaction flask, m.p. 228-230°. The

resolved diastereomer was saponified according to the literature method.[9] The 228-230° material yielded 6.0 g. of the (-) acid, m.p. 136-138°, $[a]_D^{25}$ -24.6° (c = 2.6, abs. ethanol); reported[9] - m.p. 136-137°, $[a]_D^{20}$ -23.87° (c = 23, abs. ethanol).

(±)-trans-2,3-Diphenylcyclopropanecarbonyl chloride.-- Seven grams (0.029 mole) of racemic trans-2,3-diphenylcyclopropanecarboxylic acid and 20 ml. (33.2 g., 0.28 mole) of thionyl chloride was mixed at room temperature in a flask fitted with a magnetic stirrer and a drying tube. The mixture was gently stirred for 17 hours. After about 15 minutes the acid had completely dissolved and a clear light yellow solution remained. The excess thionyl chloride was then removed on the rotary evaporator and the final traces were removed by pumping for one hour (0.2 mm.) at room temperature. A clear, deep red oil was obtained and was used directly to prepare the acid azide.

(±)-trans-2,3-Diphenylcyclopropanecarbonyl azide.-- The crude acid chloride was dissolved in 50 ml. of reagent grade acetone (dried over molecular sieve 4A) and the deep red solution was cooled to 0°. A solution of 1.91 g. (0.029 mole) of sodium azide in 18 ml. of water was cooled to 0° and added rapidly in one portion to the stirred acid chloride solution. Some immediate sodium chloride formation

was noted. The mixture was stirred for one hour at 0° followed by a two hour stirring period at room temperature. The reaction mixture was then poured into 100 ml. of water whereupon a red oil appeared. The mixture was extracted with three 30 ml. portions of diethyl ether. The deep red ether extracts were combined, extracted with two 20 ml. portions of saturated sodium bicarbonate solution and finally washed with 30 ml. of water. The ether solution was dried for six hours over a large amount of anhydrous magnesium sulfate. The acid azide was not isolated but was converted to the isocyanate.

(+)-trans-2,3-Diphenylcyclopropyl isocyanate.--A 200 ml. three-necked flask fitted with a condenser (calcium sulfate drying tube) and a pressure-compensated addition funnel was flushed with dry nitrogen for 15 minutes. Dry benzene, 95 ml., was then added and brought to reflux under the nitrogen stream. The nitrogen was disconnected and the ether solution of the crude acid azide was added dropwise over a 30 minute period. During the addition the condenser water was turned off so as to allow the ether to evaporate as soon as it came into contact with the refluxing benzene. The deep orange solution was then refluxed for 10.5 hours. The isocyanate was not isolated but was used directly to prepare the corresponding unsymmetrical urea.

(+)-trans-2,3-Diphenylcyclopropylurea.--The benzene solution of the isocyanate was cooled to 0°. The apparatus was fitted with a gas inlet tube and a magnetic stirrer. Petroleum ether, 50 ml., was added to the benzene and dry ammonia was passed into the solution for one hour. During the course of the reaction period a voluminous light tan solid appeared. Another 40 ml. of petroleum ether was added and ammonia was passed into the solution for an additional half hour. The light tan solid was filtered, washed with cold petroleum ether and air dried. The urea weighed 5.19 g. (70.0% based on racemic trans-2,3-diphenylcyclopropylcarboxylic acid), m.p. 76-97°. This material proved to be exceedingly difficult to purify. Various solvent systems were tried to effect purification but in all cases the urea oiled out of solution. It was subsequently found that the oil would solidify when scratched with a glass rod in the presence of a small amount of tert-butyl alcohol. Urea of m.p. 89-96° was obtained in this manner and repeated recrystallizations from hot tert-butyl alcohol yielded white platelets, m.p. 94.0-96.5°. Due to purification difficulties the racemic urea was not analyzed; the infrared spectrum (nujol) of the racemic urea was identical to the spectrum (nujol) of analytically pure (-)-trans-2,3-diphenylcyclopropylurea except for differences in the fingerprint region. Infrared absorptions (nujol) were observed at: 3.05 (s,

broad), 6.05 (vs), 6.3 (s), 6.5 (vs), 6.7 (s), 7.6 (w), 8.2 (vw), 8.4 (w), 8.5 (vw), 8.7 (w), 9.0 (vw), 9.3 (vw), 9.75 (m), 9.9 (w), 10.3 (m, broad), 11.0 (s), 11.6 (w), 12.0 (w), 12.6 (w), 13.0 (w), 13.3 (s), 13.55 (w), 13.9 (vw) and 14.4 (s) microns.

(±)-N-Nitroso-N-(trans-2,3-diphenylcyclopropyl)urea.--Racemic trans-2,3-diphenylcyclopropylurea (0.966 g., 3.84 mmole) dissolved in 3.0 ml. of a mixture of 70 per cent glacial acetic acid and 30 per cent acetic anhydride was cooled to 0° and magnetically stirred. Sodium nitrite (0.528 g., 7.66 mmole) in 0.6 ml. of distilled water was added to the urea solution over a 40 minute period. The clear, light green solution was then stirred at 0° for six hours. Addition of water caused the nitrosourea to precipitate as a light yellow gummy solid. This material was washed with a copious amount of water until the odor of acetic acid was no longer detectable. Grinding of the crude nitrosourea under 15 ml. of petroleum ether and subsequent filtration yielded 0.43 g. (39.8%) of a light yellow amorphous solid, m.p. 91-94.5 dec. Recrystallization of this material from a mixture of chloroform-petroleum ether (3.5:6.5) at -10° yielded 0.15 g. of a pale yellow amorphous solid, m.p. 109-110° dec. Infrared absorptions (KBr) were observed at: 2.8 (s, broad), 3.2 (w), 5.7 (vs), 5.8 (s), 6.3 (s), 6.7 (s), 6.9 (m), 7.15 (s), 7.45 (vw), 7.5 (vw),

7.9 (vw), 8.1 (vw), 9.35 (w, broad), 9.65 (w), 9.95 (m), 10.05 (m), 10.75 (m), 11.6 (w), 12.2 (m), 12.35 (w, shoulder), 13.05 (s), 13.25 (s), 14.35 (vs), and 14.8 (s) microns.

Anal. Calcd. for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.10; H, 5.47; N, 15.00.

(+)-1,3-Diphenylallene.--The procedure used was that of Jones, Grasley and Brey for obtaining 1,1-diphenylallene.[8] Phillips 99 mole per cent research grade n-heptane was used without further purification. The heptane was degassed with dry nitrogen just prior to use. Lithium ethoxide was prepared according to the literature method.[8] Sixty-seven milligrams (0.24 mmole) of racemic N-nitroso-N-(trans-2,3-diphenylcyclopropyl)urea was stirred with 2.5 ml. of n-heptane at 0° and the reaction assembly was flushed with dry nitrogen. Twenty-four milligrams (0.24 mmole) of lithium ethoxide was then added to the reaction mixture. After a reaction period of one hour, the mixture was filtered and the n-heptane was removed at 0° by a stream of dry nitrogen. The resulting white solid was dissolved in n-pentane at 0° and the solution was stored in a Dry Ice-acetone bath for 24 hours. The fluffy white solid melted at 48-50°; reported[10] for 1,3-diphenylallene: m.p. 49-51°. The ultraviolet spectrum was consistent with the literature[10] values. Infrared absorptions were observed (KBr) at: 2.9 (m), 3.3 (m), 3.4 (w), 5.19 (s), 6.3 (s), 6.7 (vs), 6.9

(vs), 7.3 (w), 7.6 (w), 8.0 (m), 8.4 (w), 8.5 (vw), 8.7 (vw), 9.4 (m), 9.8 (s), 10.9 (s), 11.35 (s, doublet), 11.9 (vw), 12.2 (w, shoulder), 12.6 (s), 13.2 (vs), 13.9 (s) and 14.4 (vs) microns.

(+)-trans-2,3-Diphenylcyclopropanecarbonyl chloride.--Four grams (0.017 mole) of (-)-trans-2,3-diphenylcyclopropanecarboxylic acid ($[a]_D^{25}$ -24.6°) was converted to the corresponding acid chloride by employing the procedure used to effect the same transformation in the racemic series. At the end of the reaction period the mixture was a light green. The removal of the thionyl chloride was accomplished at room temperature. The acid chloride was obtained as a light green microcrystalline solid. A repeat preparation on a small scale yielded a light green oil which would not crystallize. Infrared absorptions were observed (neat) at: 3.25 (m), 3.4 (w), 5.6 (vs), 6.25 (m), 6.3 (w), 6.7 (s), 6.9 (s), 7.05 (s), 7.5 (s), 7.9 (m), 8.3 (vw), 8.7 (w), 9.2 (s), 9.75 (vs), 10.4 (vs), 10.9 (s), 11.6 (m), 12.3 (s, broad), 13.25 (vs), 13.4 (s, shoulder), 13.7 (m), 14.4 (vs) and 14.9 (m); n_D^{22} 1.5887. The solid acid chloride had $[a]_D^{23.5}$ + 185° (c = 2.0, chloroform).

(+)-trans-2,3-Diphenylcyclopropanecarbonyl azide.--The procedure used was the same as that employed to effect the corresponding transformation in the racemic series. After drying over magnesium sulfate the ether solution of the acid

azide was colorless. A small portion of the ether solution was taken to near dryness and the resulting white amorphous solid was filtered. This material had a melting point of 163-166° dec. The azide had $[a]_D^{25}$ + 208° (c = 0.30, chloroform). Infrared absorptions (KBr) were observed at: 2.9 (vs), 3.2 (w), 4.2 (m), 4.4 (m), 6.2 (vs), 6.4 (vs), 6.7 (s), 6.9 (m), 8.0 (m, broad), 9.3 (vw), 9.7 (vw), 13.0 (w), 13.4 (m), 14.2 (s), and 14.4 (m, shoulder) microns.

(-)-trans-2,3-Diphenylcyclopropyl isocyanate.--The (+) acid azide was converted to the (-) isocyanate by the procedure used to effect the transformation in the racemic series. At the end of the reaction period the benzene solution was a light orange. A portion of the benzene solution was evaporated to a volume of one milliliter and petroleum ether was added to effect the precipitation of the isocyanate. The material was a white amorphous solid, m.p. 154-157°, $[a]_D^{25}$ -147° (c = 2.1, chloroform). Infrared absorptions (KBr) were observed at: 2.9 (s), 3.2 (s), 4.2 (m), 5.1 (w), 5.3 (w), 6.1 (vs, broad), 6.2 (s), 6.45 (vs), 6.7 (vs), 6.9 (m), 8.0 (m, broad), 9.3 (m, broad), 9.7 (s), 11.0 (w), 11.6 (w), 12.5 (w), 13.3 (vs) and 14.35 (vs) microns.

(-)-trans-2,3-Diphenylcyclopropylurea.--The benzene solution of the (-) isocyanate was diluted with 35 ml. of dry benzene. The clear, orange solution was cooled to 0°

and vigorously stirred with a Teflon paddle stirrer. Dry ammonia was passed into the solution and a white solid began to precipitate after ten minutes of the ammonia treatment. Ammonia was passed into the mixture for an additional 50 minutes and the white solid was then filtered off at 0°. The compound was washed with 150 ml. of cold petroleum ether. Air drying yielded 2.1 g. (49%) of an amorphous white solid, m.p. 129-131°, $[a]_D^{25}$ -95.4° (c = 0.95, abs. ethanol). Recrystallization of the urea was effected by dissolving the solid in chloroform at room temperature, adding petroleum ether to the cloud point and then storing the solution at -15° for 24 hours. Two recrystallizations in this manner gave an analytical sample, m.p. 130-131°. Infrared absorptions (KBr) were observed at: 2.8 (s), 2.9 (s), 3.2 (m), 6.0 (vs), 6.2 (s), 6.4 (vs), 6.65 (m), 6.9 (w), 7.3 (m), 7.45 (m), 7.65 (w), 8.15 (w), 9.0 (m), 9.3 (w), 9.7 (w), 9.8 (w), 11.0 (w, broad), 11.4 (w), 12.0 (w), 12.7 (m), 12.9 (w), 13.4 (s) and 14.3 (vs) microns.

Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 75.92; H, 6.35; N, 10.94.

(-)-N-Nitroso-N-(trans-2,3-diphenylcyclopropyl)urea.--(-)-trans-2,3-Diphenylcyclopropylurea, 0.80 g. (3.18 mmoles), dissolved in 9.0 ml. of a mixture of 70 per cent glacial acetic acid and 30 per cent acetic anhydride was cooled to 0° and magnetically stirred. Sodium nitrite,

0.44 g. (6.38 mmoles), in 0.5 ml. of distilled water was added to the urea solution in four equal portions over a 40 minute period. Stirring at 0° was continued for an additional three hours. The mixture was then filtered and ice chips were added to the yellow supernatant until precipitation had begun. The mixture was then stirred for 15 minutes at 0°. The pale yellow amorphous solid was filtered, washed with distilled water until the acetic acid was removed and finally washed with cold petroleum ether. After drying for two hours in a vacuum dessicator at 0.5 mm. the compound weighed 0.45 g. (56%), m.p. 114.5-115.5° dec., $[a]_D^{24}$ -193° (c = 0.95, abs. ethanol). Recrystallization from 3:1 petroleum ether-chloroform at -15° gave an analytical sample with m.p. 117.5-118°; this material was apparently unstable and did not give a satisfactory analysis. The infrared spectrum (KBr) was identical to that of the racemic compound except for minor differences in the fingerprint region.

(+)-1,3-Diphenylallene.--The (+) allene was prepared from 0.220 g. (0.78 mmole) of (-)-N-nitroso-N-(trans-2,3-diphenylcyclopropyl)urea by the same procedure used to prepare the racemic allene. The crude allene was obtained in the form of a pale yellow granular solid, m.p. 35-42°. The ultraviolet spectrum of this substance was superimposable with the spectrum of the racemic allene. Using the 255 mμ absorption (ϵ = 52,200) as the analysis peak it was

found that the allene was formed in 79.2 per cent yield. The yield of nitrogen produced in the reaction was 96 per cent, $[a]_D^{25}$ +419° (c = 0.6, abs. ethanol). The infrared spectrum (KBr) showed the same absorptions as the racemic allene except for minor differences in the fingerprint region and a weak broad peak between 5.80 and 6.00 microns. In a prior run (+) allene ($[a]_D^{24}$ + 336°) which melted at 38-51° was obtained. The infrared spectrum (KBr) of this material was superimposable with racemic allene except for very minor differences in the fingerprint region. Recrystallization of the allene from pentane at -15° gave small white needles, m.p. 52-56.5°, $[a]_D^{24}$ + 797° (c = 0.32, abs. ethanol). Reported:[10] $[a]_D^{23}$ + 2.48° (CCl_4). The infrared spectrum (KBr) of this material was identical to that of pure racemic 1,3-diphenylallene except for minor differences in the 11.0-11.5 u region.

(-)-trans-1,2-Diphenylcyclopropane.--(-)-trans-2,3-Diphenylcyclopropanecarboxylic acid (2.1 g., 8.8 mmole, $[a]_D^{19}$ -10.9°, c = 2.86, absolute ethanol; chromatographically homogeneous on a thin layer of Merck silica gel HF_{254} using ultraviolet detection and n-butanol: glacial acetic acid: water, 25:25:10 as developer), 0.2 g. copper chromite catalyst[37] and 10 ml. of quinoline (J. T. Baker, reagent grade) were introduced into a three-necked flask fitted with a gas inlet tube, a condenser topped with a calcium

sulfate drying tube and a glass-clad magnetic stirring bar. The apparatus was flushed with dry argon for 15 minutes and the mixture was then heated in an oil bath at 240° (bath temperature) for six hours. A slight argon flow and vigorous magnetic stirring were maintained throughout the reaction period. The mixture was then cooled to room temperature under a stream of argon. Sixty milliliters of ether was added and the catalyst was filtered off. The ether solution was extracted with three 20 ml. portions of water (each portion containing 8 ml. of concentrated hydrochloric acid), followed by two 20 ml. portions of 2N sodium hydroxide and finally washed with 20 ml. of saturated sodium chloride solution. The ether solution of the hydrocarbon was dried over sodium sulfate for eight hours; during the drying period the mixture was stored in the icebox under an argon atmosphere to prevent air oxidation. The ether was removed on the rotary evaporator at room temperature and 0.7 g. (43%) of the hydrocarbon was obtained. The analyses and ozonolysis (see following preparation) of this material were performed immediately to minimize oxidation of the compound. The hydrocarbon had n_D^{20} 1.5975 and $[a]_D^{20}$ -30.9° (c = 1.0, abs. ethanol); reported: n_D^{20} 1.5995,[14] optically active form: unreported. The infrared spectrum (neat) of this material showed the same absorptions with the same relative intensities as that reported[38] for the racemic

hydrocarbon. The hydrocarbon was chromatographically homogeneous on a thin layer of Merck silica gel HF_{254} using chloroform as the developer and ultraviolet detection. The compound had a Rf value of 0.70 under these conditions. Characteristic nuclear magnetic resonance absorptions were observed at 2.92 and 7.75 tau. Reported NMR spectrum:[14] 2.87 (aromatic protons) and 7.87 (benzylic protons).

Ozonolysis of (-)-trans-1,2-diphenylcyclopropane.-- The optically active hydrocarbon (0.6 g.) was dissolved in 80 ml. of glacial acetic acid. A stream of crude ozone was obtained from a Welsbach ozone generator using tank oxygen and an oxygen flow of 0.35 cubic feet per minute. The ozone stream was introduced into the magnetically stirred reaction mixture by means of a glass tube fitted with a gas dispersion frit. The ozone was passed in for 2.5 hours at room temperature. Six milliliters of 30 per cent hydrogen peroxide was then added and the clear solution was magnetically stirred for 15 hours at room temperature. The solution was then taken to dryness on the water bath. The resulting oil was treated with three 10 ml. portions of 10 per cent hydrogen peroxide, the addition of each portion followed by evaporation to dryness on the water bath. The resulting yellow oil was dissolved in water and the aqueous solution was extracted with three 8 ml. portions of 30-60° petroleum ether. The combined petroleum ether fractions

were dried over sodium sulfate and the solvent was removed with a stream of dry argon. One hundred milligrams of a white solid was obtained, m.p. 72-78°. One recrystallization from hot water yielded material with a melting point of 87.5-90°. The crystalline white solid had $[a]_D^{20}$ -5.7° (c = 1.9, abs. ethanol).[39] The infrared spectrum (nujol mull) was essentially identical to a spectrum of the racemic material (Aldrich Chemical Co., recrystallized once from hot water, m.p. 90-91.5°) except for minor differences in a few peak shapes in the fingerprint region. Analysis by thin layer chromatography (Merck HF_{254} silica gel using ultraviolet detection and butanol: glacial acetic acid: water, 25:25:10 as developer) showed identical spots for the racemic and levorotatory trans-2-phenylcyclopropanecarboxylic acid. The acid had an R_f value of 0.82 and was chromatographically homogeneous under these conditions.

Bis-(N-methyl-N-phenyl)-fumaramide.--One hundred and twenty milliliters (171 g., 1.12 mole) of fumaryl chloride (Eastman White Label) was added dropwise to a vigorously stirred solution of 486 ml. of N-methylaniline (Eastman Practical Grade) in 1.8 liters of ether (dried over molecular sieve 4A) cooled to 0°. The addition was effected over a 1.5 hour period. The mixture was then stirred for 1.5 hours at room temperature. The product was collected by filtration, washed with two liters of cold ether and dried in an oven

at 120° for one hour. The white amorphous solid was powdered and shaken vigorously with four liters of water. The product was collected by filtration, the filter cake washed with one liter of water and dried overnight in an oven at 120°. The crude amide was dissolved in 1050 ml. of hot 95 per cent ethanol and allowed to stand in the icebox for 12 hours. The white crystalline amide was collected and, after drying, weighed 253.4 g. (93%), m.p. 188.5-190°. Reported:[40] m.p. 187-188°.

Ethyl trans-2,3-bis(N-methylcarboxanilido)cyclopropane carboxylate.--One hundred and fifty grams of bis(N-methyl-N-phenyl)fumaramide was placed in a 500 ml. three-necked flask fitted with a gas inlet tube, a condenser topped with a calcium sulfate drying tube, a pressure-equalizing addition funnel and a magnetic stirrer. The apparatus was flushed with dry argon for 15 minutes and a slow argon flow was maintained throughout the rest of the reaction. The apparatus was lowered into an oil bath maintained at 205-210°. After the amide had completely melted (required approximately one hour), 58.2 g. (54 ml., 0.51 mole) of ethyl diazoacetate was added dropwise with stirring over a 135 minute period. After the addition had been completed, the deep red solution was stirred for 20 minutes while maintaining the bath temperature at 205-210°. The solution was cooled to room temperature and the resulting

dark brown tar was thoroughly ground with 400 ml. of cold ether until all of the material had solidified and no tarry material remained. The solid product was collected by filtration and the filter cake was washed with 800 ml. of cold ether. The light tan solid weighed 114 g. (58.8%) after drying and had m.p. 125-130°. The majority of the crude ester was saponified to the corresponding acid without further purification. An analytical sample was prepared by recrystallizing the ester three times from hot 50 per cent aqueous ethanol and had m.p. 139-140°. Infrared absorptions (Kel-F) were observed at: 3.3 (m, broad), 5.8 (s), 6.0 (vs), 6.3 (m), 6.7 (s), 6.9 (w), 7.0 (m), 7.25 (m) and 7.5 (m) microns.

Anal. Calcd. for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36; N, 7.36. Found: C, 69.24; H, 6.40, N, 7.58.

trans-2,3-Bis(N-methylcarboxanilido)cyclopropane-carboxylic acid.--Ethyl trans-2,3-bis(N-methylcarboxanilido)-cyclopropane carboxylate (113 g., 0.297 mole), was dissolved in 2100 ml. of absolute methanol. Methanolic potassium hydroxide, 328 ml. (50 g. of potassium hydroxide diluted to one liter with absolute methanol), was added and the solution was refluxed for three hours. The amber solution was cooled and the solvent was removed on the rotary evaporator at room temperature. The resulting amber oil was vigorously

shaken with two liters of 2N NaOH until all of the product had either dissolved or solidified. The mixture was filtered and the basic supernatant was extracted with three 500 ml. portions of chloroform. The aqueous solution was acidified with concentrated sulfuric acid to pH 2 and the cloudy, acidic solution was extracted with six 500 ml. portions of chloroform. The chloroform extracts were dried over sodium sulfate. The chloroform was removed on the rotary evaporator and the resulting amber mush was thoroughly ground in a mortar and pestle with 150 ml. of petroleum ether (20-40°). The light yellow solid was collected by filtration and the filter cake was washed with 200 ml. of 10 per cent acetone-90 per cent petroleum ether (v:v). After drying, the solid weighed 45.1 g. (25.2% overall yield from ethyl diazoacetate) and had m.p. 179-184°. The acid was recrystallized from 2700 ml. of hot acetone. After standing for 15 hours in the icebox, 3.7 g. of a white crystalline solid was obtained, m.p. 187-189°. The supernatant was reduced in volume to one liter and the solution was allowed to stand in the icebox for 48 hours. The second crop had m.p. 187-189° and weighed 31.4 g. An analytical sample was prepared by recrystallizing the crude acid three times from hot acetone. After drying, the white crystalline solid had m.p. 187-189°. Infrared absorptions (Kel-F) were observed at: 3.4 (m), 5.9 (s), 6.1 (vs), 6.2 (vs), 6.3 (vs), 6.7 (m), 6.9 (w), 7.05 (m), 7.25 (s) and 7.4 (w) microns.

Anal. Calcd. for $C_{20}H_{20}N_2O_4$: C, 68.17, H, 5.72, N, 7.95. Found: C, 68.23, H, 5.64, N, 7.73.

trans-2,3-Bis(N-methylcarboxanilido)cyclopropanecarbonyl chloride.--Ten grams (2.84 mmole) of trans-2,3-bis(N-methylcarboxanilido)cyclopropanecarboxylic acid was magnetically stirred with 20 ml. of thionyl chloride (Fisher, reagent grade) in a 500 ml. round bottom flask fitted with a calcium sulfate drying tube for 2.5 hours at room temperature. The majority of the excess thionyl chloride was removed from the light yellow solution by evaporation at water aspirator pressure. The last traces of thionyl chloride were removed by pumping on the semi-solid mass at 1 mm. for two hours. The crude acid chloride was obtained as an off-white solid, m.p. 132-138°, 10.7 g. (100%). The infrared spectrum (Kel-F mull) of the acid chloride showed significant absorptions at 5.6 u (acid chloride carbonyl, and 6.05 u (doublet, unequivalent amide carbonyls). No acid hydroxyl or acid carbonyl absorption was noted in the spectrum. The crude acid chloride was not purified but was converted directly to the corresponding acid azide.

trans-2,3-Bis(N-methylcarboxanilido)cyclopropanecarbonyl azide.--The acid chloride (2.15 g.) was dissolved in 24 ml. of anhydrous reagent grade acetone (dried over

molecular sieve 4A). The light amber solution was cooled to 0° and 0.5 g. of solid sodium azide was added. The mixture was magnetically stirred at 0° for 15 minutes and 4 ml. of an ice-cold saturated aqueous solution of sodium azide was added in one portion. The mixture was stirred at 0° for one hour. Thirty-four milliliters of distilled water was then slowly added with stirring to the azide solution. The mixture was stirred for five minutes and the resulting crystalline azide was collected by filtration and washed with a few milliliters of distilled water. After drying, the crystalline white solid weighed 0.77 g., m.p. 107-107.5° dec. with gas evolution. The infrared spectrum (Kel-F mull) of this material showed significant absorptions at 4.7 u (N_3 asymmetric stretch), 5.9 u (acid azide carbonyl) and 6.1 u (tertiary amide carbonyl). The supernatant liquid was diluted with 60 ml. of water and the aqueous solution was extracted with three 20 ml. portions of ether. The combined ether extracts were dried over sodium sulfate. Removal of the solvent on the rotary evaporator at room temperature afforded an orange oil which partially solidified when seeded with a small amount of the crystalline azide from above. The material was ground under petroleum ether (20-40°), the resulting solid collected by filtration, washed with petroleum ether and dried. The solid weighed 0.42 g. and melted 95-101° dec. with gas evolution. The

infrared spectrum was nearly identical to that of the crystalline azide obtained above. The azide crops were combined and dissolved in 100 ml. of anhydrous benzene (dried over molecular sieve 4A). After drying over a copious amount of magnesium sulfate for three hours, the azide was converted to the corresponding isocyanate by the procedure outlined below.

trans-2,3-Bis(N-methylcarboxanilido)cyclopropyl isocyanate.--The benzene solution of the azide was filtered into an argon-flushed, one liter, three-necked flask fitted with a condenser topped with a calcium sulfate drying tube and a thermometer. Xylene (Fisher, histological grade, dried over molecular sieve 4A) was added from an addition funnel until the reflux temperature was 110° (required approximately 300 ml of xylene). The solution was then refluxed for 24 hours. The isocyanate was not isolated but was converted directly to the corresponding urea as outlined below.

trans-2,3-Bis(N-methylcarboxanilido)cyclopropylurea.--The isocyanate solution from the above preparation was cooled to 0° with an ice water bath and the flask was fitted with a gas inlet tube and a teflon paddle stirrer. A rapid stream of anhydrous ammonia was passed into the vigorously stirred solution at 0°. After five minutes' reaction time,

a white solid began to precipitate. After 45 minutes total reaction time, the white solid was collected by filtration, washed with a few milliliters of cold benzene and dried. The amorphous white solid weighed 0.8 g. (38.5%) and had m.p. 203-209° dec. Upon repeating the formation of the urea from the starting acid, it was found that the yields were somewhat erratic and varied between 30.8 per cent and 40 per cent. Attempts to run the conversion on a larger scale resulted in drastically lower yields. The urea was purified by recrystallization from hot 95 per cent ethanol. The crude urea, 1.8 g. was dissolved in 35 ml. of boiling 95 per cent ethanol, treated with activated charcoal, filtered and the supernatant liquid was concentrated to 10 ml. After standing in the icebox for 18 hours, 1.15 g. of pure urea was collected, m.p. 209-210° dec. The analytical sample was prepared by recrystallizing the crude material twice from 95 per cent ethanol; m.p. 215.5-216.5° dec. Infrared absorptions (nujol) were observed at: 3.0 (m), 6.1 (vs, doublet), 6.3 (m), 6.6 (w), 6.7 (m), 7.8 (w), 8.0 (w), 8.3 (m), 8.5 (m, broad), 8.9 (s), 9.8 (w), 10.5 (m), 11.5 (w), 11.8 (w), 12.2 (w), 12.6 (w), 12.9 (s, broad), and 14.4 (s, broad). Nuclear magnetic resonance absorptions ($CDCl_3$) were observed at: 2.74, 5.35, 6.74, 7.95, 8.75 and 8.95 tau.

Anal. Calcd. for $C_{20}H_{22}N_4O_3$: C, 65.56, H, 6.05, N, 15.29. Found: C, 65.29, H, 6.20, N, 15.40.

Kinetic resolution of trans-2,3-Bis(N-methylcarboxanilido)cyclopropanecarboxylic acid.--Various attempts to resolve the acid via the quinine, quinidine, brucine, cinchonine or cinchonidine salts all failed. In all cases, using both aqueous and non-aqueous solvent systems, uncrystallizable glasses were formed. trans-2,3-Bis(N-methylcarboxanilido)cyclopropanecarbonyl chloride (6.78 g., 18.6 mmoles) was dissolved in 100 ml. of dry tetrahydrofuran (dried over molecular sieve 4A). (-)-Menthol (1.45 g., 9.3 mmoles) and 1.2 ml. (1.15 g., 9.5 mmoles) of N,N-dimethylaniline was dissolved in 100 ml. of dry tetrahydrofuran. The menthol solution was added to the acid chloride solution and the resulting light amber solution was refluxed for one hour. The solution was then diluted with 250 ml. of water and extracted with three 100 ml. portions of chloroform. The combined chloroform extracts were extracted with three 100 ml. portions of 2N sodium hydroxide. The light yellow sodium hydroxide solution was acidified with 12N sulfuric acid until a permanent cloudiness was obtained (pH 2). The acidic solution was extracted with three 100 ml. portions of chloroform and the combined extracts were dried over sodium sulfate. The solvent was removed at room temperature and the resulting oil was

triturated with 30-60° petroleum ether. The very pale yellow solid weighed 2.44 g. and had m.p. 184-189°. The solid was dissolved in 150 ml. of hot acetone, treated with activated charcoal, and the solution concentrated to 50 ml. After standing in the icebox overnight, 1.15 g. of white platelets were obtained in one crop, m.p. 186-189°, $[a]_D^{20}$ -7.8° (c = 1.4, abs. ethanol). The infrared spectrum (Kel-F) of this material was virtually identical to the spectrum of authentic, racemic acid.

(-)-Menthyl chloroacetate.--The method of McCoy[41] was employed to obtain the ester. Thirty-nine grams (0.25 mole) of l-menthol (Eastman, white label), 28.2 g. (0.25 mole) of chloroacetyl chloride (Eastman, white label) and 56.2 g. (0.28 mole) of dimethyl aniline (Fisher, reagent grade) yielded 39.6 g. (68%) of the (-) ester, b.p. 89-90° (0.7 mm.); reported:[41] b.p. 125-126° (10 mm.).

(+)-trans-1,2-Cyclopropanedicarboxylic acid.--The method used was that of McCoy[41] with modifications. Thirty-nine grams (0.144 mole) of (-) menthyl chloroacetate, 14.5 g. (0.144 mole) of methyl acrylate (Matheson, Coleman & Bell, practical grade) and 6.35 g. (0.144 mole sodium hydride) of sodium hydride dispersion in mineral oil (Metal Hydrides, Inc., 54.5% sodium hydride in mineral oil) were stirred for 16 hours with 70 ml. of anhydrous reagent grade

N,N-dimethylformamide (dried over molecular sieve 4A) in a 250 ml., three-necked flask fitted with a magnetic stirrer, thermometer and drying tube. The reaction temperature was maintained between 25-28° by adding ice chips to a water bath as required. Seventy milliliters of distilled water was added to the solution and the aqueous solution was extracted with three 50 ml. portions of benzene. The combined yellow benzene extracts were dried over sodium sulfate. The solvent was removed on the rotary evaporator and 46.5 g. of a light yellow oil was obtained. The crude ester was saponified and worked up according to McCoy's procedure.[41] The crude acid weighed 2.65 g., m.p. 162-174°. Recrystallization from hot acetonitrile yielded 1.55 g. of the acid in two crops, m.p. 174-176.5° with sintering at 167°; $[a]_D^{20}$ + 3.92° (c = 0.023, water). Reported:[41] m.p. 174-176°; reported rotation for a similar asymmetric synthesis:[42] $[a]_D^{24}$ + 8.6° → + 9.3° (water). The infrared spectrum (Kel-F) of the optically active material was virtually identical to the spectrum in the same medium of a sample of the racemic acid (m.p. 175-176°).[43]

Optically active trans-1,2-cyclopropyldicarbonyl chloride.--(+)-trans-1,2-Cyclopropanedicarboxylic acid (0.8 g., 6.16 mmole) was magnetically stirred with 8 ml. of thionyl chloride for five hours at 65-70° (bath temperature).

The excess thionyl chloride was removed by pumping on the solution at aspirator pressure for one-half hour. The clear, colorless acid chloride had n_D^{20} 1.4969 and the infrared spectrum (neat) showed a complete absence of absorptions due to the carboxylic acid group and the presence of a strong doublet centered at 5.64 u (acid chloride carbonyl). Reported:[44] n_D^{25} 1.4931.

(-)-trans-1,2-Bis(N-methylcarboxanilido)cyclopropane.--Optically active trans-1,2-cyclopropyldicarbonyl chloride (from the above preparation) was dissolved in 20 ml. of anhydrous ether (dried over molecular sieve 4A). N-Methylaniline (2.64 g., 24.64 mmole, Eastman, practical grade) was dissolved in 20 ml. of anhydrous ether and the aniline solution was added dropwise to the stirred acid chloride solution at room temperature over a 50 minute period. The mixture was then stirred for an additional 30 minutes at room temperature. The solvent was removed on the rotary evaporator and the resulting mushy solid was extracted in a Soxhlet apparatus with 100 ml. of anhydrous ether for 18 hours. The yellow ether solution was saturated with anhydrous hydrogen chloride and the resulting amine hydrochloride was removed by filtration. Removal of the ether on the rotary evaporator afforded a light orange gum which solidified when triturated with ether-petroleum ether (30-60°). The orange solid was thoroughly washed with a small

amount of cold 25 per cent ether-75 per cent petroleum ether. The resulting white solid (0.5 g.) was recrystallized from 2 ml. of hot ether. The diamide was obtained as a white crystalline solid (0.22 g.), m.p. 129-130°. $[\alpha]_D^{19}$ -3.85° (c = 2.6, ethanol). The infrared spectrum (Kel-F mull) showed no absorption in the 2.5 to 6.0 u region and exhibited a strong, sharp band at 6.1 u (tertiary amide carbonyl).

Anal. Calcd. for $C_{19}H_{20}N_2O_2$: C, 74.00, H, 6.54, N, 9.08. Found: C, 73.75, H, 6.36, N, 8.87.

Ethyl acetonedicarboxylate.--Acetonedicarboxylic acid (Light & Co., Colnbrook, England) was treated with absolute ethanol and anhydrous hydrogen chloride as prescribed in the literature method.[45] Four hundred grams (2.74 mole) of the acid yielded, after distillation, 356 gms. (64.2%) of the ester, b.p. 103-105° (2 mm.). Reported:[45] 131-136° (9-10 mm.).

3-Chloroglutaconic acid.--The procedure of Ingold and Nickolls[46] was followed with difficulty. The chloroester was obtained as a red oil. The oil was suspended in 500 ml. of 20 per cent hydrochloric acid and the mixture was boiled for 2.5 hours. At the end of the heating period the reaction mixture consisted of an amber lower layer and a light yellow aqueous layer. The amber layer was separated

and was taken up in ether. The golden yellow ether solution was washed with water and dried over calcium chloride. After standing overnight at -10°, 28.4 gms. of an amorphous white solid was obtained, m.p. 114-127°. The solvent was removed from the supernatant and the red oil was allowed to stand at -10° for 20 days. The resulting white crystals were dried and had m.p. 135-139° (10.6 gms.). The 114-127° material was recrystallized from ether-chloroform (1:2.5) at -10°. A white solid with m.p. 132-136° was obtained (9.3 gms.). The infrared spectrum of this material was identical to that of the 135-139° material. The second and third crops both had m.p. 135-139° and had a combined weight of 10.3 gms. Reported: m.p. 129°,[47] m.p. 141-142°.[48]

1,3-Pentadienedioic acid (glutinic acid).--The procedure of Vander Zanden[48] was slightly modified. 3-Chloroglutaconic acid, 20.5 gms. (m.p. 135-139°, 0.124 mole), was dissolved in 385 ml. of 1N sodium hydroxide. The clear, light yellow solution was allowed to stand at room temperature for five hours. Fifty milliliters of 10 per cent sulfuric acid was then added (congo red endpoint). The clear acidic solution was extracted with six 200 ml. portions of ether. The ether extracts were combined and dried over calcium sulfate. Solvent removal at room temperature afforded 9.87 gms. (62%) of a white amorphous solid, m.p. 141-145°. Reported: m.p. 158.5°,[48] 149-150°.[49] The infra-

red spectrum (KBr) of this material was identical to that reported[50] by Agosta.[51]

1,3-Pentadienedioyl chloride (glutinyl chloride).--Glutinic acid, 0.25 g. (1.95 mmole), and 0.83 g. of phosphorous pentachloride (4.0 mmole) was suspended in 15 ml. of anhydrous benzene. Hydrogen chloride evolution was noted immediately. The suspension was stirred for four hours and the benzene was then removed from the resulting orange solution on the rotary evaporator. The infrared spectrum (neat) of the resulting crude orange oil showed a strong peak at 5.1 u (allene) and a very strong peak at 5.6 u (acid chloride carbonyl); no absorptions due to carboxylic acid carbonyl or hydroxyl were noted. Attempts to prepare the crude acid chloride using thionyl chloride gave a product which did not possess the 5.1 u absorption.

Ethyl cis-1,2-dimethyl-3(trans)-cyclopropanecarboxylate.--Ninety grams (150 ml., 1.61 moles) of cis-2-butene (Matheson, C.P. grade) was condensed in a three-necked cylindrical reaction vessel fitted with a large Dry Ice condenser and a quartz-jacketed, Hanovia type L, 450 watt, high pressure (immersion type) mercury arc lamp with an outer pyrex filter sleeve. The cooling jacket of the immersion assembly was cooled to -23° by circulating cold methanol which was cooled in a copper coil immersed in a carbon

tetrachloride-Dry Ice slush bath. The outer portion of the reaction assembly was cooled to -23° with a similar slush bath. Four grams (0.035 mole) of freshly distilled ethyl diazoacetate (b.p. 26-26.5° at 1.5 mm.) was added to the butene followed by 0.2 gm. of anhydrous copper sulfate and 0.2 gm. of electrolytic copper powder. The light yellow solution was irradiated for 10 hours. The butene was allowed to evaporate at room temperature and the resulting yellow oil was taken up in ether and filtered. The ether was removed in vacuo and the resulting yellow oil was molecularly distilled (25°, 2 mm.) yielding 3.16 grams of a yellow liquid. The product was dissolved in 25 ml. of ether and the solution, along with 25 ml. of water, was introduced into a 200 ml. flask fitted with a dropping funnel and a magnetic stirrer. The mixture was cooled to 0° and vigorously stirred. Forty milliliters of 5 per cent sulfuric acid was cautiously added dropwise over a 1.5 hour period. The ether layer became colorless after approximately one-half of the acid had been added and nitrogen evolution ceased at this point. The clear, colorless layer was separated and the aqueous layer was extracted with two 10 ml. portions of ether. The ether extracts were combined and washed with 10 ml. of concentrated sodium bicarbonate solution and finally with 10 ml. of saturated salt solution. After drying over molecular sieve 4A, the ether was removed

at room temperature. This procedure yielded 0.4 gm. of a straw-colored liquid. GLC on the A-350-B instrument using a 10 foot x 3/8 inch column packed with 20 per cent SF 96 on 60/80 mesh firebrick with a column temperature of 128° and a helium flow rate of 4.8 ml/min showed one major peak with a retention time of 15 minutes and five minor peaks with shorter retention times. The material with retention time of 15 minutes was isolated by preparative scale GLC using the above conditions. The infrared spectrum (neat) of this material was identical to that reported[52] for methyl cis-1,2-dimethyl-3(trans)-cyclopropanecarboxylate except for bands at 7.3 u (medium), 11.6 u (weak) and 12.9 u (medium) which were present in the ethyl ester spectrum and a band at 10.77 u reported for the methyl ester but absent in the ethyl ester spectrum. Analytical GLC using the 600-B instrument with a 1/8 inch five foot column packed with 5 per cent SE 30 on 60/80 mesh Chromosorb W at 92° and inlet pressure of 10 p.s.i.g., showed a major peak with retention time of 2.4 minutes and a minor peak at 1.8 minutes. The minor peak was 1.5 per cent of the mixture by area integration.

Anal. Calcd. for $C_8H_{14}O_2$: C, 67.57, H, 9.92. Found: C, 67.30; H, 9.72.

Ethyl trans-1,2-dimethyl-3-cyclopropanecarboxylate.--The method was the same that was employed to obtain ethyl

cis-1,2-dimethyl-3(trans)-cyclopropanecarboxylate from cis-2-butene and diazoacetic ester. A solution of 17.3 g. (0.15 mole) of ethyl diazoacetate in 90 g. (150 cc., 1.61 moles) of trans-2-butene (Matheson, C.P. grade) gave, after partial irradiation and decomposition of the unreacted diazoacetic ester, 3.5 g. of a straw-colored liquid. GLC using the same conditions as in the corresponding run with cis-2-butene showed four minor peaks and a major peak with a retention time of 13.4 minutes. GLC preparative isolation of a sample from the 13.4 minute peak was accomplished and the infrared spectrum (neat) of the ester was identical to that published[52] for methyl trans-1,2-dimethylcyclopropane-3-carboxylate except for peaks at 7.41 (m), 12.87 (m), and 13.65 (w) microns which were present in the spectrum of the ethyl ester and a band at 10.88 microns which was reported for the methyl ester spectrum but which was absent from the spectrum of the ethyl ester.

Anal. Calcd. for $C_8H_{14}O_2$: C, 67.57; H, 9.92; Found: C, 67.33; H, 9.93.

Tri-n-butyltin hydride.--The procedure of Van der Kerk et al.[53] was employed. One hundred forty grams (0.43 mole) of tri-n-butyltin chloride[54] gave, after distillation through a 1 x 10 cm. Vigreaux column, 78.0 gms. (62.5%) of the hydride, b.p. 91-93° (1.5 mm.); reported[53] b.p. 76-81° (0.7-0.9 mm.).

trans-1,1-Dibromo-2,3-dimethylcyclopropane.--The method of Skell and Garner[20] was used. The bromoform used was distilled just prior to use, b.p. 35-37° (1.1 mm.). Commercial potassium tertiary butoxide was used (Chemical Intermediates and Research Laboratories, P.O. Box 146, Cuyahoga Falls, Ohio). The amount of trans-2-butene (Matheson, C.P. grade) used was increased to approximately 3.5 moles to facilitate efficient stirring. One hundred grams of bromoform (0.4 mole) yielded 70.8 grams (78.7%) of the dibromide as a clear, colorless liquid, b.p. 72-72.5° (35 mm.), n_D^{19} 1.5146. Reported:[20] b.p. 64.0° (23 mm.), $n_D^{25.1}$ 1.5108.

1-Bromo-trans-2,3-dimethylcyclopropane.--The method employed was that of Seyferth, Yamazaki and Alleston[55] to prepare 1-bromo-2,2-dimethylcyclopropane. In a 200 ml. three-necked flask fitted with a thermometer, magnetic stirrer and pressure-equalizing dropping funnel topped with a gas inlet tube was placed 54.8 g. (0.24 mole) of 1,1-dibromo-trans-2,3-dimethylcyclopropane. The apparatus was flushed with argon for 15 minutes. Seventy grams of tri-n-butyltin hydride (0.24 mole) was added to the stirred liquid over a 75 minute period while maintaining the temperature at 30-40° by external cooling. The clear, colorless solution was then stirred for an additional hour at 30-35°. The reaction mixture was fractionated on a

1 x 10 cm. Vigreaux column and, after a 3 ml. forerun, 27.8 g. (78%) of a clear, colorless liquid was collected, b.p. 107-109° (760 mm.). Redistillation using the above column afforded 21.4 g. of the bromide, b.p. 111-112° (760 mm.); n_D^{19} 1.4576. Infrared (neat) absorptions at: 3.34 (s), 6.90 (s), 7.25 (m), 7.66 (w), 8.10 (s), 10.5 (w), 10.7 (m), 10.83 (m), 12.51 (m), and 12.9 (w) microns. Nuclear magnetic resonance absorptions were observed (neat) at: 7.16, 7.26, 7.30, 7.38, 8.75, 8.85, 8.94, and 9.27 (broad, complex multiplet) tau.

Anal. Calcd. for C_5H_9Br: C, 40.32, H, 6.04, Br, 53.58. Found: C, 40.12, H, 6.02, Br, 53.81.

trans-2,3-Dimethylcyclopropanecarboxylic acid. A. From ethyl trans-1,2-dimethyl-3-cyclopropanecarboxylate.--The ester (2.1 g., 0.0148 mole) was refluxed for 22 hours with 15 ml. of absolute methanol containing 3.9 g. (0.07 mole) of potassium hydroxide. Water (15 ml.) was added followed by 25 ml. of 10 per cent hydrochloric acid. Solid sodium hydroxide was then added until the light yellow solution was slightly basic to litmus. The methanol was removed at room temperature by means of a rotary evaporator and the resulting aqueous solution was acidified to the congo red endpoint with 10 per cent hydrochloric acid. The solution was then extracted continuously for 20 hours. The

light yellow ether extract was dried over magnesium sulfate and the ether was removed at room temperature on a rotary evaporator. The acid was obtained as a pale yellow liquid, 1.45 g. (86.1%). The compound was characterized as the para-phenylphenacyl derivative. An analytical sample was obtained after two recrystallizations from hot absolute ethanol and melted 84-85°.

Anal. Calcd. for $C_{20}H_{20}O_3$: C, 77.90; H, 6.54. Found: C, 78.07; H, 6.77.

B. From 1-bromo-trans-2,3-dimethylcyclopropane.-- The apparatus used was dried in an oven at 120° for one hour and assembled while hot in a stream of dry argon. One hundred milliliters of anhydrous ether (dried over molecular sieve, type 4A), 3.26 g. (0.134 g. atom) of magnesium turnings and a few crystals of resublimed iodine were introduced into a 200 ml. three-necked flask fitted with a pressure-equalizing addition funnel, a large Graham condenser and a magnetic stirrer. Twenty grams (0.134 mole) of 1-bromo-trans-2,3-dimethylcyclopropane was dissolved in 30 ml. of anhydrous ether and the clear solution was introduced into the addition funnel. The mixture was stirred with a glass-clad stirring bar and 5 ml. of the bromide solution was introduced. Approximately one-half milliliter of methyl iodide was then added and the mixture was heated to reflux with a hot water bath. Refluxing continued after removal

of the water bath and the bromide solution was added dropwise to the vigorously stirred mixture over a 1.5 hour period. A gentle reflux was maintained throughout the addition period with no external heating. After the bromide had been added, the mixture was heated at reflux for 1.5 hours. The carbonation was carried out using a modification of Hussey's procedure.[56] A one liter, three-necked flask was fitted with a pressure-equalizing addition funnel, a Teflon paddle stirrer and a drying tube. The apparatus was flushed with dry argon and 300 g. of Dry Ice (finely pulverized) and 150 ml. of anhydrous ether was added to the flask. The light brown Grignard reagent was decanted from unreacted magnesium and transferred to the addition funnel. The Dry Ice-ether slurry was vigorously stirred and the Grignard reagent was added over a 20 minute period. The mixture was then stirred until the Dry Ice had evaporated and 50 g. of ice and 25 ml. of 6N hydrochloric acid was added with stirring. The layers were separated and the aqueous layer was continuously extracted with ether for 48 hours. The yellow ether extract was combined with the original ether layer and the solution was extracted with three 75 ml. portions of 2N sodium hydroxide. The clear, colorless aqueous solution was acidified with 6N sulfuric acid to pH 2 and continuously extracted with ether for 27 hours. After drying over sodium sulfate, the ether was removed at room tempera-

ture using the rotary evaporator and 4.75 g. (31.2%) of a pale yellow liquid was obtained. The para-phenylphenacyl derivative of this material, after recrystallization from absolute ethanol, melted 84-85° and had an infrared spectrum (nujol) which was superimposable with the spectrum of the same derivative of the acid prepared in A. The infrared spectrum of the acid (neat) showed absorptions at: broad OH centered at 3.4 (m), 5.9 (s), 6.9 (m), 7.25 (vw), 7.45 (vw), 7.7 (m), 8.15 (m), 8.65 (vw), 8.95 (vw), 9.15 (w), 9.40 (w), 10.3 (w), 10.7 (w), 11.8 (vw), 12.1 (w), 12.85 (w), and 13.9 (vw) microns.

Resolution of trans-2,3-dimethylcyclopropanecarboxylic acid.--The racemic acid (3.80 g., 0.033 mole) was dissolved in 40 ml. of hot absolute ethanol. Quinine (10.8 g., 0.033 mole) was dissolved in 60 ml. of hot absolute ethanol. The hot quinine solution was poured into the acid solution and the resulting clear solution was heated on the water bath for 10 minutes. The light amber solution was allowed to stand at room temperature for three hours and was then filtered. The ethanol was removed on the rotary evaporator and the resulting amber gum was dissolved in 30 ml. of hot acetone. After standing at room temperature for one hour crystallization had begun and the mixture was put in the icebox for two hours. The resulting precipitate

was collected by filtration and washed with approximately 100 ml. of cold acetone. The white salt was dried in an oven at 60° for 0.5 hour. The diastereomer weighed 9.6 g. and had m.p. 117-119.5°, $[a]_D^{19}$ -123° (c = 2.6, abs. ethanol). The salt was suspended in 50 ml. of distilled water and 50 ml. of 2 per cent methanolic sodium hydroxide was added. Fifty-five milliliters of methanol was then added to completely dissolve the salt. The methanol was removed on the rotary evaporator and the mixture was allowed to stand at room temperature for one hour to insure complete solidification of the precipitated quinine. The quinine was removed by filtration and the basic supernatant was acidified to pH 2 with concentrated sulfuric acid. The aqueous solution of the acid was continuously extracted with ether for 38 hours. After drying the ethereal solution with sodium sulfate, the solvent was removed at room temperature on the rotary evaporator. Two and one-half grams of the acid was obtained as a straw-colored liquid, $[a]_D^{23}$ + 0.701° (neat, d = 1 dm.). The infrared spectrum (neat) of this material was superimposable with the spectrum of the racemic material. The solvent was removed from the mother liquor of the original crystallization and the resulting amber oil was subjected to the above methanolic sodium hydroxide neutralization procedure. Continuous extraction of the acidified aqueous solution with ether for 36 hours and drying of the

ether solution with sodium sulfate yielded 0.62 g. of the levorotatory acid, $[a]_D^{20}$ -1.46° (neat, d = 1 dm.). The infrared spectrum (neat) was superimposable with that of the dextrorotatory acid. Both the dextrorotatory and levorotatory acids were chromatographically homogeneous on a thin layer of Merck silica gel HF_{254} using butanol:acetic acid:water (25:25:10) as the developer and ultraviolet detection. The acid had a Rf value of 0.27 under these conditions. Using the above procedure, a large scale resolution starting with 16.0 grams of racemic acid yielded 5.75 g. (m.p. 120-122°) of diastereomer as a first crop and 37.1 g. (m.p. 118.5-120.5°) as a second crop. The combined crops had $[a]_D^{20}$ -131° (c = 2.7, abs. ethanol). Regeneration of the acid from the combined crops gave 10.9 g. of optically active acid, $[a]_D^{17}$ -4.73° (c = 4.5, abs. ethanol).

In an attempt to increase optical purity, 2.5 g. of acid was treated with quinine as before and the first crop of diastereomer had m.p. 120.5-122.5°, $[a]_D^{20}$ -126° (c = 3.35, abs. ethanol). Recrystallization of this solid from acetone yielded diastereomer with m.p. 121.5-124.0°, $[a]_D^{20}$ -132° (c = 3.15, abs. ethanol). Recrystallization of the 121.5-124° material from acetone yielded diastereomer with m.p. 119.5-125.0°, $[a]_D^{20}$ -126° (c = 2.9, abs. ethanol). Acid was regenerated from the 119.5-125.0° material and had

$[a]_D^{20}$ -4.66° (c = 3.6, abs. ethanol). Recrystallization of the first crop of diastereomer (m.p. 120.5-122.5°) was attempted from the following solvents: chloroform, dimethylformamide, methylene chloride, tetrahydrofuran, diethyl ether, ethyl acetate, acetonitrile and benzene. Only the last three solvents were found to be suitable and none of them altered the melting range appreciably; ethyl acetate, m.p. 121-125°; acetonitrile, m.p. 120.5-123.5°; benzene, m.p. 119-124°.

Optically active trans-2,3-dimethylcyclopropanecarbonyl chloride.--Twenty-five milliliters of thionyl chloride was added cautiously over a 25 minute period to 10.0 g. (0.087 mole, $[a]_D^{19}$ -4.73°) of trans-2,3-dimethylcyclopropanecarboxylic acid. The light brown solution was then stirred at room temperature for 13 hours. The majority of the excess thionyl chloride was removed by pumping at aspirator pressure for one hour. The brown liquid was distilled using a 1 x 10 cm. Vigreaux column; 9.05 g. (78%) of a clear liquid was obtained, b.p. 149-150.5°, $[n]_D^{21}$ 1.391. The acid chloride was immediately converted to the corresponding acid azide using the procedure outlined below.

Optically active trans-2,3-dimethylcyclopropanecarbonyl azide.--Nine grams (0.068 mole) of optically active trans-2,3-dimethylcyclopropanecarbonyl chloride was dissolved

in 47 ml. of anhydrous acetone (dried over molecular sieve 4A) at 0°. An ice cold solution of sodium azide (12.8 g., 1.95 mole in 31 ml. of distilled water) was poured in one portion into the magnetically stirred acetone solution. The resulting yellow solution was stirred at 0° for 45 minutes. The light yellow acetone layer (upper layer) was separated and the aqueous layer was extracted with three 20 ml. portions of ether. The aqueous solution was then extracted with three 20 ml. portions of acetone. The acetone extracts were combined and dried over magnesium sulfate for 12 hours. The combined ether extracts were also dried over magnesium sulfate for 12 hours. The acetone was removed on the rotary evaporator at room temperature. A light yellow viscous liquid was obtained along with a yellow lower layer with a volume of approximately 2 ml. The mixture was taken up in 50 ml. of ether and the insoluble yellow layer was extracted with three 20 ml. portions of ether. All of the ether extracts, including the one from the original extraction, were combined and extracted with two one milliliter portions of saturated sodium bicarbonate solution. The light yellow ether solution was dried over a copious amount of magnesium sulfate for 2.5 hours with magnetic stirring. The acid azide was not isolated but was converted directly to the corresponding isocyanate by the procedure outlined below.

Optically active trans-2,3-dimethylcyclopropyl isocyanate.--A 500 ml. three-necked flask was fitted with a pressure-equalizing dropping funnel and a condenser topped with a calcium sulfate drying tube. The apparatus was flushed with dry argon for 15 minutes and 250 ml. of anhydrous benzene (dried over molecular sieve 4A) was introduced into the flask and brought to reflux. The condenser water and the argon flow were turned off and the filtered ether solution of the azide was added dropwise over a one-half hour period. When all of the ether had evaporated and the solution temperature had reached 76°, the condenser water was turned on and the light yellow solution was refluxed for 16 hours. The isocyanate was not isolated but was converted directly to the corresponding urea as outlined below.

(+)-trans-2,3-Dimethylcycloproplurea.--The light yellow solution of optically active trans-2,3-dimethylcyclopropanecarbonyl azide was cooled to 0° in an ice-water bath and ammonia was passed into the vigorously stirred isocyanate solution. Precipitation of a white solid was noted after five minutes of the ammonia treatment; the ammonia was passed into the solution for a total of 45 minutes. Filtration of the product and washing with a small amount of cold benzene yielded 4.9 g. (54%) of a white solid, m.p. 131-138°. The urea was recrystallized from 100 ml. of hot acetone;

2.92 g. of white platelets were obtained in two crops, m.p. 149.5-151.5°, $[a]_D^{20}$ + 3.45° (c = 3.1, abs. ethanol). An analytical sample was prepared by recrystallizing the purified urea twice more from acetone; the sample had m.p. 150.0-151.5°. The compound showed infrared absorptions (Kel-F) at: 2.9 (vs), 3.1 (s), 3.3 (w), 3.4 (m), 6.05 (vs), 6.25 (s), 6.7 (s), 6.9 (w), 7.1 (w), 7.25 (w), 7.35 (w) and 7.55 (m) microns. Thin layer chromatography on Merck HF_{254} silica gel using ultraviolet detection and chloroform as solvent showed one spot with an R_f value of 0.37.

Anal. Calcd. for $C_6H_{12}N_2O$: C, 56.23; H, 9.44; N, 21.86. Found: C, 56.00; H, 9.27; N, 22.01.

(+)-N-Nitroso-N-(trans-2,3-dimethylcyclopropyl)urea.--(+)-trans-2,3-Dimethylcyclopropylurea ($[a]_D^{20}$ + 3.45°, 2.4 g., 0.0187 mole) and 0.151 g. (0.0187 mole) of anhydrous sodium acetate was suspended in 25 ml. of anhydrous ether and the resulting white slurry was cooled to -55°. Dinitrogen tetroxide (1.86 g., 0.02 mole) in 7.43 ml. of ether was introduced into the stirred urea suspension. The blue suspension was stirred at -55° for 45 minutes. The resulting lemon yellow solution was warmed to room temperature, washed with three 5 ml. portions of 5 per cent sodium bicarbonate solution followed by washing with 5 ml. of water

and dried over magnesium sulfate. Removal of the solvent at room temperature on the rotary evaporator yielded 2.5 g. (81.5%) of a lemon yellow powder, m.p. 74-77° dec. Recrystallization was effected by dissolving the nitrosourea in 10 ml. of chloroform, adding 150 ml. of petroleum ether (30-60°) and allowing the solution to stand for 20 hours in the icebox. Filtration of the product yielded 2.0 grams of a fluffy, lemon yellow crystalline solid, m.p. 76.5-77.5° dec., $[a]_D^{21}$ + 2.69° (c = 4.2, abs. ethanol). The nitrosourea was chromatographically homogeneous on a thin layer of Merck silica gel using chloroform as developer and ultraviolet detection and had an R_f value of 0.17 under these conditions. Infrared absorptions were observed (nujol) at: 2.9 (m, broad), 5.85 (s), 6.3 (w), 7.7 (w, broad), 8.2 (vw), 9.0 (w, broad), 9.5 (w), 9.7 (m, broad), 10.5 (s), 10.8 (m), 11.9 (m, doublet), 12.9 (m, broad), and 14.3 (m, broad) microns. Nuclear magnetic resonance absorptions ($CDCl_3$) were observed at: 7.92 (complex multiplet), 8.75, 8.84, 9.13, and 9.23 tau. Two recrystallizations from chloroform-petroleum ether gave an analytical sample, m.p. 77.5-78° dec.

Anal. Calcd. for $C_6H_{11}N_3O_2$: C, 45.84; H, 7.05; N, 26.73. Found: C, 45.75; H, 7.20; N, 26.52.

Reaction of (+)-N-Nitroso-N-(trans-2,3-dimethylcyclopropyl)urea with lithium ethoxide; 1,3-dimethylallene.--One and one-half grams (9.5 mmole) of (+)-N-nitroso-N-(trans-2,3-dimethylcyclopropyl)urea ($[a]_D^{21}$ + 2.69°) was dissolved in 50 ml. of triethyleneglycol (dried over molecular sieve 4A). The magnetically stirred yellow solution was cooled to 0° and 0.93 g. (9.5 mmoles) of lithium ethoxide alcoholate[8] was added from a solids addition tube. After a five minute induction period, nitrogen evolution was noted. Gas evolution had ceased after 45 minutes of stirring at 0° and the solution was clear and nearly colorless. A total of 178 ml. of gas was collected (83.5%). The reaction flask was put on a high vacuum system and pumped on at 0.02 mm. for two hours. The volatile material was condensed out in a 1.5 ft. x 2 in. through trap cooled in liquid nitrogen and located between the reaction vessel and the mechanical pump. Control experiments showed that water and ethanol dissolved in triethylene glycol were essentially non-transferable under these conditions. The volatile material in the through trap was back transferred to a 15 ml. graduated centrifuge tube. The volume of the collected liquid was approximately 0.25 ml. The liquid had $n_D^{21.5}$ 1.4289 and the infrared spectrum (gas) showed peaks at 3.3 (vs), 5.02 (m), 6.8 (s), 7.2 (m), 7.7 (m), and 11.3 (m, broad peak) u. Reported for 1,3-dimethylallene: n_D^{20}

1.4266,[57] n_D^{25} 1.4204,[58] and (C=C=C) 5.06 u.[58]

(+)-2,2-Diphenylcyclopropanecarboxylic acid.--Forty-five grams (0.189 mole) of racemic 2,2-diphenylcyclopropanecarboxylic acid[8] was dissolved in 310 ml. of hot 95 per cent ethanol. Anhydrous quinine, 60.8 g. (0.190 mole) was dissolved in 375 ml. of hot 95 per cent ethanol. The two hot solutions were poured together and the resulting amber solution was heated on the steam bath for five minutes. After cooling to room temperature over a three hour period the resulting white needles were air dried; the material weighed 39.8 g., m.p. 185.5-188.0°. The diastereomeric mixture was then dissolved in 495 ml. of hot 95 per cent ethanol. The clear solution was allowed to cool to room temperature over a 2.25 hour period. Filtration and air drying of the resulting solid yielded 32.5 g. of white needles, m.p. 189.5-191.0°. The diastereomer was suspended in 400 ml. of distilled water and 400 ml. of 2 per cent ethanolic sodium hydroxide was added. The ethanol was then removed on the rotatory evaporator. The resulting precipitate of quinine was filtered off and the supernatant was acidified with 3N hydrochloric acid. Filtration and air drying yielded 12.4 g. of the acid, m.p. 150-151.5°, $[a]_D^{23.5}$ + 229° (c = 1.24, $CHCl_3$). Reported[59] m.p. 150-151°, $[a]_D^{23.5}$ + 230° ($CHCl_3$).

(+)-2,2-Diphenylcyclopropanecarbonyl chloride.--Eight grams (0.034 mole) of (+)-2,2-diphenylcyclopropanecarboxylic acid ($[a]_D^{23.5}$ + 229°) was magnetically stirred with 22.9 ml of thionyl chloride for 17 hours at room temperature. The excess thionyl chloride was removed on the rotary evaporator and the final traces were removed by pumping on the solid mass at 0.5 mm. for three hours. The acid chloride was obtained in 91 per cent yield as a light green microcrystalline solid, m.p. 92-96°, $[a]_D^{25}$ + 183° (c = 1.5, $CHCl_3$).

(+)-2,2-Diphenylcyclopropanecarbonyl azide.--(+)-2,2-Diphenylcyclopropanecarbonyl chloride (7.85 g., 0.03 mole, $[a]_D^{25}$ + 183°) was dissolved in 57 ml. of acetone (dried over molecular sieve 4A) and the light green solution was cooled to 0°. A solution of 2.18 g. of sodium azide in 20.5 ml. of water was cooled to 0° and added in one portion to the magnetically stirred acid chloride solution. The resulting amber mixture was stirred at 0° for one hour and then stirred at room temperature for two hours. The reaction mixture was then poured into 100 ml. of water and the mixture was extracted with three 35 ml. portions of ether. The combined ether extracts were washed with two 25 ml. portions of saturated sodium bicarbonate solution followed by two 20 ml. portions of water and finally dried

over magnesium sulfate for 3.5 hours. A small portion of the ether solution was withdrawn and the solvent removed on the rotary evaporator. A few milligrams of the azide were obtained as a white solid, m.p. 218-220° dec., $[a]_D^{25}$ + 217° (c = 0.55, $CHCl_3$).

(-)-2,2-Diphenylcyclopropyl isocyanate.--A 200 ml. three-necked flask fitted with a condenser (topped with a calcium sulfate drying tube) and a pressure-compensated addition funnel was flushed with dry nitrogen for 15 minutes. Dry benzene, 105 ml. was then added and brought to reflux under the nitrogen stream. The nitrogen was disconnected and the ether solution of (+)-2,2-diphenylcyclopropanecarbonyl azide from the preceding preparation was added dropwise to the refluxing benzene over a 30 minute period. During the addition the condenser water was turned off so as to allow the ether to evaporate rapidly. After the addition period, the solution was heated until the temperature of the solution reached 76°. The condenser water was then turned on and the cherry red solution was refluxed for 10.5 hours. The solution was cooled to room temperature and a small portion was withdrawn. Addition of 30-60° petroleum ether to this portion precipitated the isocyanate as a light yellow solid, m.p. 195-197° dec., $[a]_D^{25}$ -178° (c = 2.0, $CHCl_3$). The remainder

of the isocyanate solution was converted directly to (+)-2,2-diphenylcyclopropylurea.

(+)-2,2-Diphenylcyclopropylurea.--The cherry red solution of (-)-2,2-diphenylcyclopropyl isocyanate was cooled to 0° and vigorously stirred with a Teflon paddle stirrer. Dry ammonia was passed in for two hours. No precipitation was noted at this point; the solution was diluted to a total volume of 100 ml. with dry benzene. While maintaining the solution at 0°, cold petroleum ether was added with stirring until a brown gum started to precipitate. Stirring at 0° was continued for 15 minutes. Scratching with a glass rod caused the gum to solidify. The lumps were carefully broken up and the solid was filtered off. The resulting white solid was thoroughly powdered with a spatula and was then washed with a copious amount of cold petroleum ether. The yield was 6.4 g. (75.6%), m.p. 144.5-147.5°. Recrystallization from aqueous ethanol yielded 4.3 g. of the urea in two crops, m.p. 146.5-148.5°, $[a]_D^{25}$ + 52.1° (c = 1.8, abs. ethanol). The infrared spectrum ($CHCl_3$), was superimposable with the spectrum of authentic racemic material.[8]

(+)-N-Nitroso-N-(2,2-diphenylcyclopropyl)urea.--The procedure used was that of Darryl Muck[60] for preparing the racemic nitroso compound. Treatment of 1.85 g. of

(+)-2,2-diphenylcyclopropylurea ($[a]_D^{25}$ + 52.1°, c = 1.8, abs. ethanol) with one equivalent of dinitrogen tetroxide at -50° in anhydrous ether yielded 1.85 g. of the crude nitrosourea. Recrystallization at -10° in 30-60° petroleum ether-chloroform (2:1) yielded 1.35 g. in one crop (65%) of pale yellow crystals, m.p. 107-107.5° dec. Further recrystallization did not alter the melting point. The compound had $[a]_D^{21}$ + 350° (c = 2.6, abs. ethanol) and was chromatographically homogeneous (R_f = 0.146) on a thin layer of Merck silica gel using chloroform as developer. The infrared spectrum (chloroform) of the material was superimposable with that of authentic racemic material.[8]

Reaction of (+)-N-Nitroso-N-(2,2-diphenylcyclopropyl)-urea with lithium ethoxide in diethyl fumarate.--One gram of (+)-N-nitroso-N-(2,2-diphenylcyclopropyl)urea ($[a]_D^{21}$ + 350°) dissolved in 20 ml. of diethyl fumarate was treated with lithium ethoxide at 0° according to the literature procedure.[8] Isolation and purification of the product using the published procedure[8] gave the expected pyrazoline with an infrared spectrum (nujol) which was superimposable with authentic racemic pyrazoline.[8] Rotation analysis (c = 5.3, DMF) showed the pyrazoline to be optically inactive.

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BIOGRAPHICAL SKETCH

John Walter Wilson, Jr. was born December 2, 1936, at Los Angeles, California. In June, 1954, he was graduated from John Marshall High School, Los Angeles, California. From 1957, until 1959, Mr. Wilson served as a research assistant in the laboratories of Professor Jerome A. Berson at the University of Southern California. In February, 1961, he received the degree of Bachelor of Arts (Chemistry) from the University of Southern California. He was awarded the degree of Master of Science (Chemistry) from the University of Southern California in June of 1962. From July, 1962 until the present time he has pursued studies toward the degree of Doctor of Philosophy at the University of Florida.

This dissertation was prepared under the direction of the chairman of the candidate's supervisory committee and has been approved by all members of that committee. It was submitted to the Dean of the College of Arts and Sciences and to the Graduate Council, and was approved as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

August 14, 1965

Ernest H. Cox
Dean, College of Arts and Sciences

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